No. 2014-1416

United States Court of Appeals For The Federal Circuit

FERRING B.V.,
Plaintiff-Appellee,

V.

WATSON LABORATORIES, INC. - FLORIDA
Defendant-Appellant,

AND

APOTEX, INC. AND APOTEX CORP.,
Defendants.

Appeal from the United States District Court for the District of Nevada
In Nos. 3:11-cv-00481-RCJ-VPC, 3:11-cv-00485-RCJ-VPC,
3:11-cv-00853-RCJ-VPC, 3:11-cv-00854-RCJ-VPC, 3:12-cv-01953-RCJ-VPC,
and 2:12-cv-01941-RCJ-VPC, Judge Robert Clive Jones.

Defendant-Appellant's Opening Brief

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May 1, 2014

CERTIFICATE OF INTEREST

Counsel for Defendant-Appellant Watson Laboratories, Inc. – Florida, certifies the following:

1. The full name of every party or amicus represented by me is:

Watson Laboratories, Inc. – Florida.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

N/A

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Watson Laboratories, Inc. – Florida (a Florida corporation) is wholly owned by Andrx Corporation (a Delaware corporation), which is a wholly-owned subsidiary of Actavis, Inc. (a Delaware Corporation).

Actavis, Inc. is wholly-owned by Actavis plc, an Irish Public Company.

By virtue of this arrangement, Actavis plc, a publicly held corporation, owns more than 10% of Watson Laboratories, Inc. – Florida.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

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May 1, 2014

s/ Christopher J. Sorenson
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STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5(a), no appeal in or from the same civil action in the lower court was previously before this or any other appellate court.

Pursuant to Federal Circuit Rule 47.5(b), there are cases known to be pending in this or any other court that will directly affect or be directly affected by this Court's decision in the pending appeal. The present case is an appeal from *Ferring v. Watson Laboratories, Inc. – Florida*, Case Nos. 3:11-cv-481, 3:11-cv-853, and 2:12-cv-1935 (D. Nev.). For pretrial proceedings and trial these cases were consolidated with *Ferring v. Apotex*, Case Nos. 3:11-cv-485, 3:11-cv-854 and 2:12-cv-1941 (D. Nev.), with Case No. 3:11-cv-481 designated as the lead case. These cases involve the same patents-in-suit but different defendants and different accused products.

The district court entered final judgment against Apotex on March 24, 2014. (Case No. 3:11-cv-481, Doc. No. 518.) Ferring appealed, and that case is proceeding as Case No. 14-1377 (Fed. Cir.). The Federal Circuit declined to enjoin Apotex from selling its product pending appeal, and expedited the briefing in that case. (Case No. 14-1377, Doc. Nos. 21 & 23.)

The district court entered final judgment against Watson on April 14, 2014. (Case No. 3:11-cv-481, Doc. No. 524.) Watson appealed, and that case was assigned Case No. 14-1416 (Fed. Cir.). On April 17, the Federal Circuit

consolidated the cases for appeal. (Case No. 14-1377, Doc. Nos. 35 & 36.) On April 18, the Federal Circuit *sua sponte* deconsolidated the cases, setting Case No. 14-1416 for an expedited briefing schedule and oral argument before the same panel that is hearing Case No. 14-1377 at 10 a.m. on June 10, 2014. (Case No. 14-1377, Doc. No. 37.)

This case is also related to another case filed by Ferring against Watson in the District of Nevada. In *Ferring v. Actavis, Inc., Watson Laboratories, Inc., Andrx Corp., Watson Laboratories, Inc. – Florida, and Watson Pharma, Inc.*, Case No. 3:13-cv-477, Ferring alleges infringement of the patents-in-suit in this case as well as a related patent, U.S. Patent No. 8,478,005. (Case No. 3:13-cv-477, Doc. No. 1.) Watson's request to dismiss or stay that case is currently pending. (Case No. 3:13-cv-477, Doc. No. 17.)

This case is also related to another case filed by Ferring against Apotex in the District of Nevada. In *Ferring B.V. v. Apotex, Inc. and Apotex Corp*., Case No. 3:13-cv-595 (D. Nev.), Ferring alleges infringement of the '005 patent. (Case No. 3:13-cv-595, Doc. No. 1.)

JURISDICTIONAL STATEMENT

The district court had jurisdiction under 28 U.S.C. §§ 1331 and 1338(a). On April 15, 2014, Watson timely filed a notice of appeal from the district court's April 14, 2014 final judgment. (Doc. Nos. 524-525.) This Court has jurisdiction under 28 U.S.C. § 1295(a)(1).

STATEMENT OF THE ISSUES

1a. The district court concluded that cores with hardness of 17kp and greater and coated commercial tablets with core hardness of 17kp and greater infringed under 271(e). Under 271(e), infringement must be based on a review of all materials submitted in support of the ANDA. Did the district court err in its 271(e) analysis by refusing to consider "minor amendments" to the ANDA, which do not allow the manufacture of Watson's cores with a hardness of 17kp?

1b. 10-35% or 5-50% of the total weight of each claimed dosage form must be "a material that modifies the release of the active pharmaceutical ingredient" in water. Did the district court err in reading out this central limitation when it found infringement by (a) Watson's immediate-release cores, where no ingredient modifies the release of the active pharmaceutical ingredient and (b) Watson's coated commercial product with a coating that comprises only 2.9% of the weight of the tablet?

1c. Each claim requires a specific "in-vitro dissolution release rate of the tranexamic acid or pharmaceutically acceptable salt thereof, when measured by the USP 27 Apparatus Type II Paddle Method." There is no dispute that of the hundreds of samples tested, every single core lacked the claimed release rate, with

only a few isolated anomalies among the coated commercial products tested even arguably falling within the claimed release profile. Did the district court err in its determination that both the cores and coated commercial products met the claimed release profile under 271(a) and 271(e)?

2a. Did the district court err in granting an injunction under 271(a) and 271(e)(4)(B) without considering the equitable factors set forth in *eBay*?

2b. Did the district court err in concluding a resetting order injunction under 271(e)(4)(A) is mandatory in all cases?

3. The prior art disclosed 500mg tranexamic acid tablets approved to treat heavy menstrual bleeding, and the use of modified release materials with pharmaceutical dosage forms was known. Did the district court err in finding the claims to a 650mg tranexamic acid tablet nonobvious because "nobody produced or studied a higher tablet?"

STATEMENT OF THE CASE

This is a patent infringement case. The relevant procedural history is discussed above in the Statement of Related Cases and below in the Statement of the Facts. The district court issued several published decisions in this case:

- 2012 U.S. Dist. LEXIS 23616 (02/24/2012) (consolidating lawsuits, striking surreplies and defenses);
- 2012 U.S. Dist. LEXIS 95737 (07/11/2012) (denying motion to strike experts);
- 2012 U.S. Dist. LEXIS 108822 (07/30/2012) (reopening dismissed case);
- 2013 U.S. Dist. LEXIS 17536 (02/06/2013) (construing claim terms);
- 2013 U.S. Dist. LEXIS 33877 (03/11/2013) (denying objection to court order);
- 2013 U.S. Dist. LEXIS 58125 (03/25/2013) (denying motions for stay, hearing, and reply);
- 2013 U.S. Dist. LEXIS 75342 (05/28/2013) (granting motion to amend invalidity contentions, denying motion to amend infringement contentions);
- 2013 U.S. Dist. LEXIS 168072 (11/03/2013) (denying motions to file reply, granting-in-part motion to limit testimony, denying other motions);
- 2014 U.S. Dist. LEXIS 38391 (03/24/2014) (denying motion to reconsider injunction);
- 2014 U.S. Dist. LEXIS 48368 (04/07/2014) (denying motion for TRO, setting hearing).

STATEMENT OF THE FACTS

I. Background.

A. The use of tranexamic acid to treat heavy menstrual bleeding was known throughout the world for decades.

Tranexamic acid is a compound that was used around the world for the treatment of heavy menstrual bleeding ("HMB") since at least the 1970s—long before the patents-at-issue here existed. (A2798, 4:16-19; A13382-98; A13629-37; A14498-523; A13399-401; A11511-26; A12515-22; A771.)

Patients were treated using two 500mg tablets, taken either two or four times per day, which provided a total daily dose of 2000-4000mg of tranexamic acid. (A13629-34; A13383; A13387-90; A13393-94; A12518; A14498; A14514; A11519; A790-91; A827-29; A11727; A11808.) The prior art tablets were both coated and uncoated, and were made with ingredients common to the pharmaceutical industry. (A835:13-837:6; A13636-37; A11490-534; A834-37.) The prior art also disclosed exactly how quickly and for how long tranexamic acid would enter the blood stream, after the prior art tablets were ingested. (A13636; A13399-401; A12518; A13384; A13389; A11498; A11503; A11508; A14509-10; A829-31.) It was also recognized that some patients taking the prior art tablets reported gastro-intestinal side effects, especially at higher doses. (A11517; A13631; A12519; A14510; A784-85; A881-82.) The prior art even recognized

that "[a] modified dosage in patients with decreased renal function will further decrease the incidence of gastrointestinal side effects." (A14517.)

B. The use of certain amounts of polymers to modify the release of active pharmaceutical ingredients was also well-known.

The use of various pharmaceutical ingredients to alter the release of an active ingredient in a dosage form has also been known for decades. (A14430-63; A14528-44; A14055-70; A14657-718; A14479-89.) For instance, a polymer known as methocel (or hypromellose) was commonly used for various purposes in pharmaceutical formulations. (A14528-38.) At certain viscosities and amounts, this polymer was known to slow the release of an active ingredient. (A14444; A14530; A14535; A868; A1769-70; A981-85.) At different viscosities and amounts, it was also known to bind ingredients in a tablet, but not slow the release of an active ingredient. (A14530; A14535; A14444.) The prior art also recognized that tranexamic acid could be used in a modified-release form. (A14481; A14517.)

II. Development and approval of 650mg tranexamic acid tablets.

A. Xanodyne assembled clinical data from the prior art and filed its first provisional application before conducting any clinical trials.

In March of 2003, researchers from Xanodyne recognized a commercial opportunity to introduce a tranexamic acid product into the U.S. for the treatment of HMB. (A11726-31; A783:8-12; A2629, 32:18-23.) The researchers were well-aware of the tranexamic acid formulations used to treat HMB around the world.

(A801; A872-73; A2630-31; A2635-40.) They based their 650mg formulation on the prior art tablets. (A790-91; A833-34.) They relied in-part upon the known effectiveness and safety of the prior art formulations to obtain FDA approval. (A2433 at 232-33; A2345 at 105; A2389-90 at 57-59; A12262-79.)

In fact, one Xanodyne researcher, Dr. Heasley (later named as one of the inventors of the patents-in-suit) admitted that the dosage regimen for treating HMB with tranexamic acid was well-known: 3000mg-6000mg, given three to four times a day, using two or three 500mg tablets per dose. (A780-81; A884-86; A891:10-19; A844-85.) Another researcher and named inventor, Dr. Moore, testified that before any formulation was made by Xanodyne, they were aware that "the [preferred] dose of tranexamic acid for menorrhagia [HMB] is 1 to 1.5 grams three or four times daily." (A2643, 89:21-89:24; A11808; A12701-02.)

Dr. Moore also testified that it was known, well before any application for the patents-in-suit was filed, that three times daily dosing was preferred for patient compliance, because a patient need only remember to take "one pill a day or two pills a day versus four." (A784:3-8; A2636-37 at 59-63.) Dr. Heasley also testified that gastrointestinal issues had been observed with the use of higher doses of tranexamic acid. (A881-22.)

The pharmacodynamic properties of tranexamic acid were so well-known that the researchers, in fact, mathematically predicted the maximum concentration

of the drug that would reach the blood stream ("C_{max}") using a hypothetical "modified release" version of tranexamic acid. (A894:13-895:18; A897:18-898:11; A893:10-24; A901-02; A904-05.) Using commonly available tools, they also predicted the time at which the maximum concentration would occur in the blood stream ("T_{max}"). (A904:15-904:13.) These predictions were made before a single patient was given a 650mg tranexamic acid tablet, later claimed in the patents-in-suit. (A894-95.)

Xanodyne relied on the prior art formulations to obtain FDA approval, informing the FDA on March 21, 2003, that "[i]n Europe, tranexamic acid has been marketed for more than three decades for the treatment of . . . menorrhagia [HMB]." (A11729.) Xanodyne, eager to avoid having to repeat clinical studies already conducted by others, also provided the FDA with several articles summarizing clinical studies on tranexamic acid, including an article concluding that "tranexamic acid is safe and effective in reducing menstrual blood loss" and teaching the "appropriate dosing of tranexamic acid in menorrhagia [HMB]." (*Id.*; A11765-84; A11806-14.)

On September 29, 2003, Xanodyne again met with the FDA and proposed developing "a modified release tablet dosage form of tranexamic acid to treat heavy menstrual bleeding" for approval. (A11983.) It also told the FDA that it

formulated a 650mg reference tablet,[1] an "immediate release tablet with dissolution properties comparable to the [prior art] Cyklo-f tablet." (*Id.*) Xanodyne contracted with Mikart "to develop and optimize a formulation that will be adequate for" its long term clinical trials. (*Id.*; A789:6-11.) Within two months, Mikart employees had not only developed, but finalized the tranexamic acid tablets claimed in the patents-in-suit. (A868:2-15; A11621-37.)

B. Xanodyne's clinical trials failed to demonstrate any improvement in "side effects" compared to the prior art.

Xanodyne began its clinical trials hoping that it might be able to establish that its 650mg tablets would reduce some of the side effects compared with the prior art tablets, and that the FDA would allow it to call its 650mg tablets "modified release." (A11983-84; A12011-14.) Neither goal was achieved. (A2664-65 at 173-74; 2671-75 at 201-15.) The FDA would not allow Lysteda to be sold as a "modified release" product, because it is not what the FDA considers a "modified release" tablet. (A12540; A2421 at 185; A12546.) Further, patients receiving the "modified release" 650mg tablets reported gastrointestinal side effects, including nausea and diarrhea. (A12827; A2673-74 at 206-10.) Indeed, Lysteda's FDA-approved label includes a listing of side effects classified as "abdominal pain," including nausea and diarrhea reported by patients taking

[1] A reference tablet is necessary for the type of New Drug Application filed with the FDA by Xanodyne, as they sought to rely upon the efficacy and safety testing of the prior art. (A2389-90 at 57-60; A2433 at 232-33; A2345 at 105.)

Xanodyne's tablets. (A2424-25 at 195-99; A11536; A2100-02; A12951; A12956; A12969.) During trial, no clinical evidence that the claimed formulation actually reduced side effects in comparison with the prior art was presented. Indeed, the only clinical evidence presented at trial showed that the prior art "immediate release" tablets had the same side effect profile as patients receiving placebo tablets. (A13399-401; A13385; A13392; A880.)

C. The patents-in-suit.

At the same time it was developing Lysteda, Xanodyne filed several patent applications. (A2914-15; A2969-70; A3028-30.) The three patents-in-suit—U.S. Patent Nos. 7,947,739 (issued May 24, 2011), 8,022,106 (issued September 20, 2011), and 8,273,795 (issued September 25, 2012)—share similar specifications, underwent similar prosecutions, and all have a common ancestor application, filed on March 4, 2004. (A2914-68.) All of the patents-in-suit claim to be bioequivalent to "immediate release" 650mg tranexamic acid tablet disclosed therein. (A2814, 35:8-10; A2864, 35:4-6; A2907, 24:28-30.)

Each of the specifications of the patents-in-suit also list the ingredients of a 650mg "immediate release" tablet, which includes ingredients that (without dispute) do not function to delay the release of tranexamic acid. (A2812-14; A2862-64; A905-07; A2103-06.) Among the ingredients listed in the immediate release dosage form is a certain amount and grade of hypromellose. (A2103-04.)

Each independent claim of the patents-in-suit is drawn to an "oral dosage form" or "formulation" that has three basic elements: (1) 650mg tranexamic acid, (2) about 10% to about 35% or about 5% to about 50% of a "modified release material," and (3) a specified dissolution release rate in water, measured by the USP 27 Apparatus Type II Paddle Method. (A2831; A2880-81; A2913.) Claim 1 of the '795 patent, for example, claims a formulation where "modified release material is present in an amount from about 5% to about 50% by weight of the formulation." (A2913.) The same claim recites that "when measured by a USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5º C" ("USP Water Test") a certain amount of tranexamic acid will be released from the formulation at different points in time. (A2913.) For instance, once the dosage form has been in the apparatus for 90 minutes, "not less than about 50% by weight of the tranexamic" is released. (A2913.) While the independent claims of the patents-in-suit are not identical, the differences between the claims are insubstantial:

'739 Claim 1	'106 Claim 1	'795 Claim 1
modified release material about 10% to about 35% by weight	Same as 739 patent	modified release material about 5% to about 50% by weight
Modified release material comprises list of certain polymers	Same as 739 patent	
		tranexamic acid about 50% to about 95% by weight
		method of treating menorrhagia
	dosage form is suitable for administration on a two or three times a day basis	two oral dosage forms
	Less than about 40% released at about 15 minutes	Same as 106 patent
Less than about 70% released at about 45 minutes	Same as 739 patent	Same as 106 patent
	Not less than about 50% released by about 90 minutes	Same as 106 patent
About 100% released by about 120 minutes		

(A14814.)

As proclaimed during prosecution, the claims are "directed to a formulation of tranexamic acid that has *both* a specific composition *and* a specific release profile." (A10734; A9195.) The patents-in-suit explain that "[a] 'modified release oral dosage form' for purposes of the present invention is an oral dosage form which releases the active ingredient . . . in a manner that is slower than an immediate release oral dosage form" when measured by the USP Water Test. (A2853, 14:21-27.) The patents-in-suit also define "immediate release" dosage forms to be "a dosage form which releases all of active ingredient (e.g., tranexamic acid) included therein without about 45 minutes when measured in vitro" utilizing the USP water test. (A2803, 14:20-25; A2853, 14:15-20; A2900, 9:58-63.)

No specification of any patent-in-suit discloses, as an alleged invention, a tranexamic acid formulation with an immediate release core, coated with a pH-dependent coating that does not dissolve in water as claimed by the patents-in-suit. (A1699:3-10; A1698:14-1699:10; A2124:9-2127:4.)

The asserted dependent claims of the patents-in-suit include five additional limitations. These general limitations include (1) an amount of tranexamic acid, (2) an amount or form of modified release material, (3) water dissolution release rates measured by the USP Water Test, (4) pharmacokinetic elements, and (5) a kind of dosage form. (A2831-32; A2880-83; A2913.)

III. Because Lysteda was not the first approved tranexamic acid product, the FDA awarded Ferring only three years of market exclusivity.

The FDA-approved Xanodyne's tranexamic acid formulation set forth in New Drug Application No. 02-2430 on November 13, 2009. (A14854-77.) Ferring bought the Lysteda product from Xanodyne shortly thereafter. (A2533-34.) Because it was not the first tranexamic acid product that had been deemed safe and effective by the FDA (A758:12-21), Lysteda was granted only three years of market exclusivity. (A812:21-815; A2433.) This FDA-granted exclusivity expired on November 13, 2012. (A2533 at 160-61.)

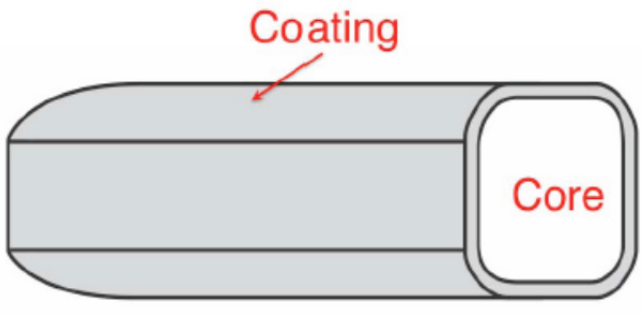
Ferring now sells its 650mg tranexamic acid tablets in the U.S. under the trademark Lysteda®. Lysteda has never been marketed as a "modified release" product, because the FDA does not consider the product to be "modified release."

(A12540; A2421 at 185; A12546.) Lysteda has never been marketed as a formulation with a better side effect profile than the 500mg prior art tablets, because no clinical study establishing such a claim was ever conducted. (A2664-65 at 173-74; A2671 at 201.) Ferring also licensed a generic version of its product to a third party, which launched its product on January 7, 2013. (A14852.)

IV. Watson designed around Ferring's patents with its ANDA and separately-patented accused products.

On July 23, 2010, almost a year before the first of the patents-in-suit issued, Watson filed Abbreviated New Drug Application ("ANDA") No. 20-2093, seeking FDA approval to market its 650mg tranexamic acid tablets. (A14830-31.) Although the patents-in-suit issued after Watson filed its ANDA, Watson was aware of, and designed around, embodiments within a published application that eventually issued as the '795 patent. (*See* A2196:15-18; A2200:5-9.)

Watson's tablets are made of an immediate release core (like the prior art) surrounded by a pH-dependent coating that resists dissolution in water (i.e. the mouth/esophagus) but dissolves immediately in acidic conditions, such as the stomach:



(A14727; A14545-51; A14074; A13836-37; A1605:9-23; A1613:8-1615:10; A1617:1-8; A1592:23-1593:21; A1630:8-1634:14.) The use of a pH-dependent coating allows for easier swallowing. (A1630:21-1631:3; A1631:12-17; A13504.)

In communications with the FDA, Watson explained that the pH-dependent coating dissolves in acidic conditions: "Eudragit EPO dissolves in 0.1N HCl and tranexamic acid is subsequently released." (A14074.) Watson further explained that the coating does not readily dissolve in water: "as the Eudragit EPO does not dissolve above pH 5, drug release in the oral cavity and the esophagus is prevented *in vivo*." (A14074.) As stated in the ANDA, "[Watson]'s formulation was designed to be slow in water." (A13845.) Watson was awarded U.S. Patent No. 8,597,683 for its separately patentable tranexamic acid product design over the patents-in-suit. (A14545-51.)

In Watson's initially filed ANDA, the hardness range for the cores was specified to be 13-20kp. (A1424; A13885.) "kp" is an abbreviation for "kiloponds," and is a measure of a tablet's hardness. (A1591:20-1592:4.) Nearly two years after filing its ANDA application, Watson began working on its ANDA

product to confirm the ability to scale the batch size to commercial manufacturing quantities. (A1635-40; A13912-13; A14088-89). During this process, Watson developed final specifications designed to ensure a robust and uniform tablet coating was applied. (A1642-46; A2085-86; A2088-95.) Watson also specified that the hardness target of the core portion of its tablets to be 15kp, and established a tightened range of hardness to be 13kp-16kp. (A14089.)

On August 29, 2012, Watson submitted a request for final approval to the FDA, and included a summary of additional changes made to its specifications, made as a result of its scale-up activities. This summary included modifications to the manner in which its cores were made. (A13912-68.) Among the modifications was an increase in the amount of alcohol used during granulation, and a further amendment to its hardness specification to maintain a target hardness of 15kp, with a range of 13kp to 17kp:

3. The following changes have been made based on data and observations made during scale up activities:
   a. The amount of additional alcohol has been adjusted (5.01 kg to 16.41 kg).
   b. The comil, chopper and mixer speeds are now specified or ranges added to ensure consistency from batch to batch.
   c. The tank pressure range has been added to assure increased safety.
   d. The total spray time range has changed from 2 - 5 minutes to 2 – 4 minutes.
   e. The ranges for alcohol addition time and mixing time have been adjusted.
   f. The blend time was adjusted based on the number of revolutions used for the exhibit batch.
   g. For consistency, the amount Lactose Monohydrate, NF Modified Spray Dried (Lactose 316 Fast Flo) to be added to the Colloidal Silicon Dioxide, NF (Cab-O-Sil M5P) is now specified (5.174 kg). The Colloidal Silicon Dioxide is manually mixed with Lactose Monohydrate in a polybag for 2 minutes to avoid loss of this excipient due its low bulk density.

Watson Item # 191163 (Tranexamic Acid Tablets, 650 mg - Core)

1. The hardness limit has been tightened to 13 kp – 17 kp with a target of 15 kp.

(A13920 (emphasis added); A14734; A1425-38.)

Watson also amended the master batch record[2] for its compression step (the point during manufacture of the product where the core ingredients are compressed together) to include an instruction for the operator of the compression machine to monitor each commercial lot, and to adjust the hardness to maintain a hardness level below 16kp:

> **Note: If required, adjust compression machine to maintain tablet hardness below 16 kp.**

(A14186; A14189; A14196; A14198; A14567; A14569; A14576.)

Watson's final ANDA product was approved as an immediate release core tablet, with a pH-dependent coating that resists dissolution in water. (A13506.) The coating is 2.9% by weight of the total weight of the tablet. (A1700-01; A13977.) A certain grade and amount of hypromellose is used in the core of the Watson tablet design as a binder. (A1583:8-1584:3; A1626:23-1630:7; A1575-76; 1580.)

On December 27, 2012, Watson received final approval from the FDA to market its product. (A13789-92.) Watson announced this approval publicly on January 3, 2013, stating "Watson intends to begin shipping product immediately." (A14848-49.) Ferring did not move to enjoin the launch of Watson's generic product.

[2] A "master batch record" is essentially a detailed set of instructions for each step of the manufacturing process. (A1648:6-18.)

Consistent with Watson's approved ANDA specification, there was no evidence at trial showing Watson ever made or sold a commercial tablet with a core hardness of 17kp. (A1149:18-23.) Indeed, Ferring's expert testified at trial that he reviewed all executed manufacturing records for Watson's commercial products, and found that they "were manufactured at low hardness levels well below 17kp." (A2077; A2075:14-20; *see also* A1149-50.) The only evidence at trial that Watson ever made any tablet with 17kp hardness was found in the archives of Watson's early development records, reflecting early experimental work done long before Watson's ANDA was filed, and even longer before its final commercial manufacturing specifications were set. (A991; A1618-19; A14840-47.)

V. Lawsuit.

Ferring sued Watson for infringement in a series of lawsuits starting in 2012, ultimately asserting independent claim 1 and dependent claims 4-5, 8-10, and 12-13 of the '739 patent, independent claim 1 and dependent claims 5-8, 15-16, 18-19, 30-37, and 40-41 of the '106 patent, and independent claim 1 and dependent claims 5-6, and 8-10 of the '795 patent. Those lawsuits were consolidated into this case. Ferring asserted that both Watson's cores (uncoated tablets) and its final coated tablets infringed the patents-in-suit.

Watson defended on the basis of non-infringement, and that all asserted claims of the patents-in-suit were invalid as obvious. Watson also asserted (in the alternative) that all asserted claims are invalid for lacking written description.

A. At trial, Watson established its cores dissolved far faster in water than claimed, and its final coated products dissolved far slower.

Watson conducted extensive testing on samples of cores and coated products from its commercial lots. The results established that Watson's core dissolves much faster than the claimed release rates. (A14216-34; A14259-89; A14762-68.) For example, all three independent claims of the patents-in-suit do not permit more than about 70% of the tranexamic acid to be released within about 45 minutes in the USP Water Test. (A2831; A2880-81; A2913.) Of the 180 cores tested, each and every one released about 100% of its tranexamic acid in 45 minutes. The data is as follows:

WATSON IN-HOUSE TESTING: CORES @ 45 MINUTES

Data from WTX 1278

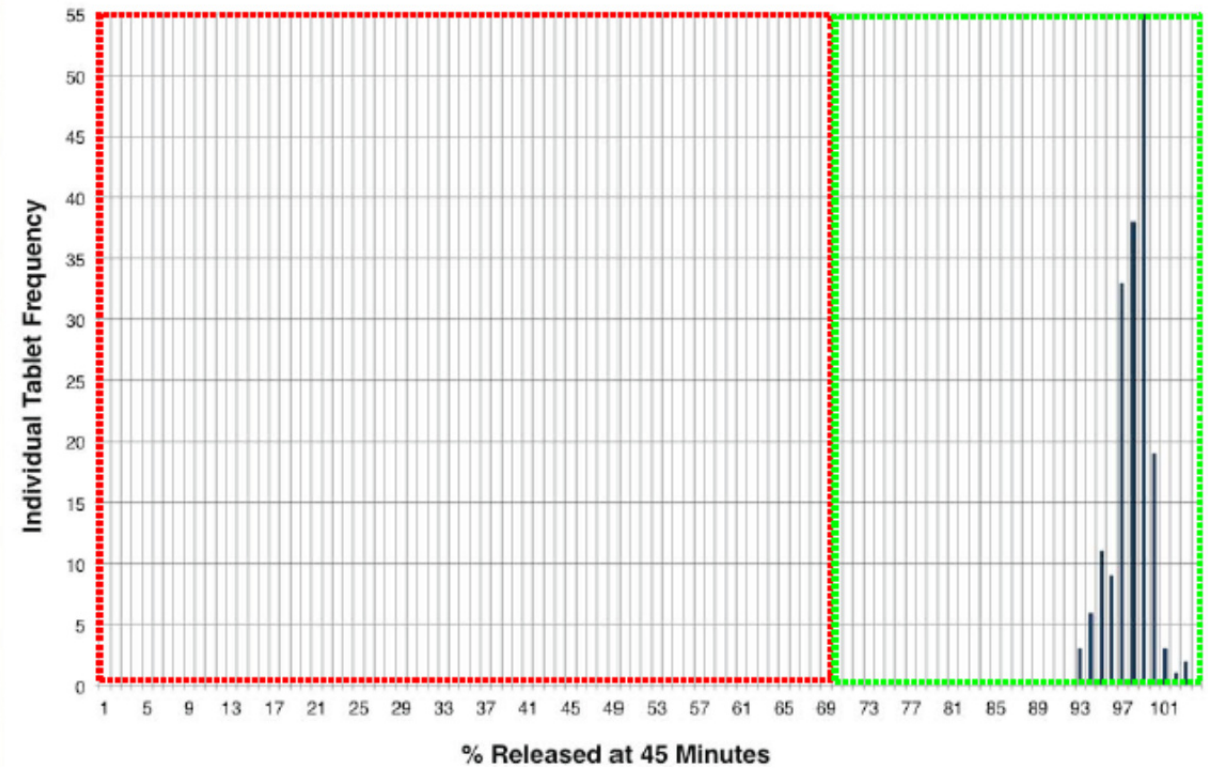
	VB2	VB3	VB4	COM1	COM2	COM3	COM4	COM5	COM6	COM7	COM8	COM9	COM10	COM11	COM12
Time (min)	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45
Sample															
1	98	100	96	100	100	100	99	99	100	101	101	98	98	100	100
2	98	99	94	101	100	99	98	99	98	96	101	98	100	100	100
3	99	100	96	100	101	101	100	99	100	96	100	100	100	99	99
4	99	99	95	99	100	101	100	100	100	101	100	100	95	100	100
5	98	99	97	100	101	101	100	98	99	101	100	98	100	103	102
6	99	99	96	99	99	101	98	100	98	102	101	98	100	100	100
mean	99	99	96	100	100	101	99	99	99	99	100	99	99	100	100
%RSD	0.4	0.6	1.0	0.6	0.5	0.8	1.1	0.8	1.0	2.7	0.4	1.0	1.9	1.3	1.0

AAI TESTING: CORES @ 45 MINUTES

Data from WTX 1281

	VB2	VB3	VB4	COM1	COM2	COM3	COM4	COM5	COM6	COM7	COM8	COM9	COM10	COM11	COM12
Time (min)	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45
Sample															
1	98	99	94	100	101	100	98	97	98	99	97	99	99	96	102
2	98	97	95	99	98	100	98	96	101	96	98	98	99	97	101
3	97	98	100	99	100	98	99	99	99	98	98	101	100	99	100
4	99	97	95	99	98	98	96	99	98	99	100	99	101	100	100
5	100	96	95	100	100	100	97	99	100	100	98	100	99	104	95
6	97	96	94	99	101	100	104	98	98	98	100	99	98	100	100
mean	98	97	95	100	100	99	99	98	99	98	98	99	99	99	100
%RSD	1.3	1.2	2.2	0.6	1.3	1.1	2.7	1.1	1.2	1.3	1.4	1.0	0.9	2.9	2.2

(A14766; *see also* A14762; A14764.) As shown below, none of the tested cores meets the claimed dissolution profile at 45 minutes (shown in red):



(A14754 (color added).) The reliability of this testing data, and the accuracy of the tables reproduced above, was not disputed by Ferring.

Because there is no dispute that Watson's ANDA product was designed to behave far differently in water than claimed in the patents-in-suit, Ferring based its infringement case on a few anomalies in Watson's testing results from samples taken of its coated commercial lots. The '106 patent and '795 patent, for example, require "*not less* than about 50%" of the tranexamic acid to release in the USP Water Test in about 90 minutes. (A2881, 69:16-19 (emphasis added); A2913, 35:47-49.) Of the 180 commercial (coated) tablets tested, 176 released *far less* than 50% of tranexamic acid at 90 minutes:

WATSON IN-HOUSE TESTING: COATED @ 90 MINUTES

Data from WTX 1278

	VB2	VB3	VB4	COM1	COM2	COM3	COM4	COM5	COM6	COM7	COM8	COM9	COM10	COM11	COM12
Time (min)	90	90	90	90	90	90	90	90	90	90	90	90	90	90	90
sample															
1	31	31	28	31	31	34	31	31	31	29	27	31	34	28	33
2	36	31	30	31	31	33	32	32	31	30	28	32	33	29	31
3	31	30	31	32	28	36	63	31	30	28	32	31	31	31	30
4	32	29	31	27	30	36	36	35	31	29	29	34	30	31	30
5	36	30	28	30	32	33	57	34	32	29	33	33	33	31	31
6	32	31	28	28	27	36	38	35	31	29	28	33	33	32	32
mean	33	30	29	30	30	35	43	33	31	29	29	32	32	30	31
%RSD	7.4	2.5	5.3	6.7	6.6	4.6	31.9	5.2	2.0	1.6	7.9	4.1	5.0	4.7	3.7

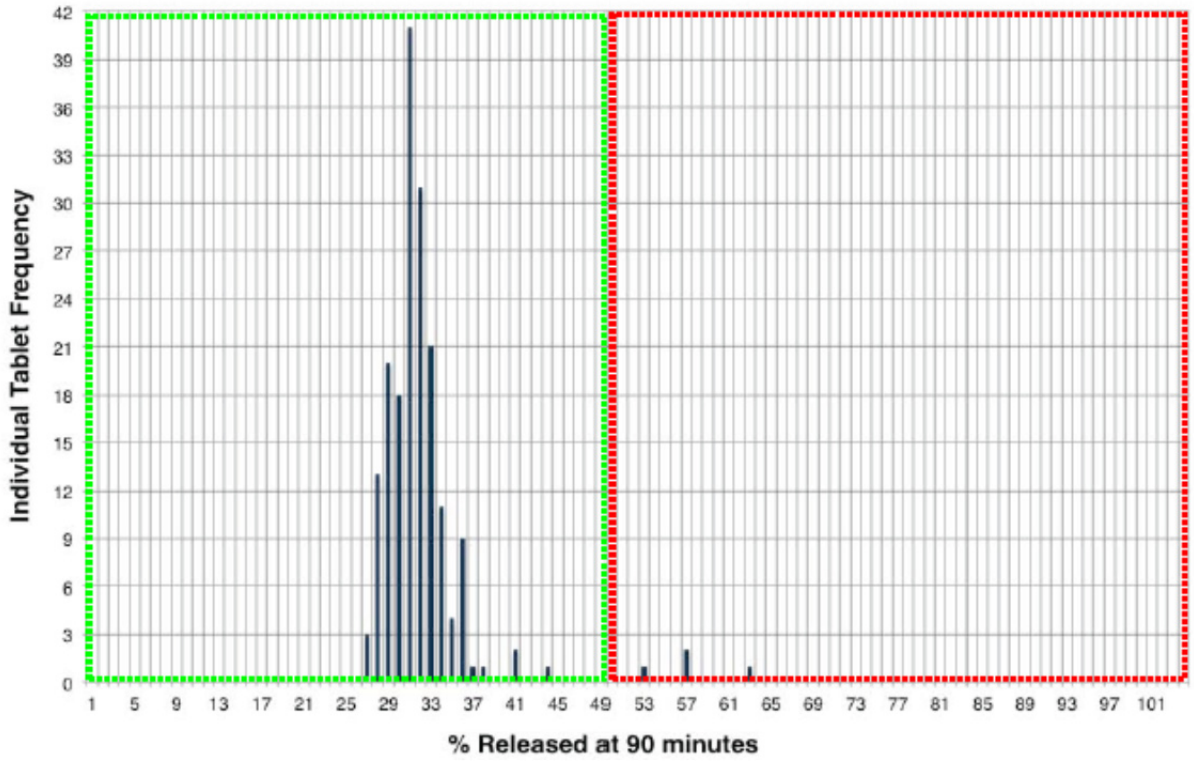
AAI TESTING: COATED @ 90 MINUTES

Data from WTX 1281

	VB2	VB3	VB4	COM1	COM2	COM3	COM4	COM5	COM6	COM7	COM8	COM9	COM10	COM11	COM12
Time (min)	90	90	90	90	90	90	90	90	90	90	90	90	90	90	90
sample															
1	32	31	31	29	31	53	32	31	31	32	29	33	31	32	32
2	35	31	35	34	28	44	33	29	31	30	32	33	32	30	31
3	41	31	32	41	29	34	33	32	32	32	32	29	32	31	32
4	34	30	28	33	28	36	30	29	32	32	31	33	31	29	31
5	36	34	33	34	28	57	34	34	33	32	29	32	32	30	33
6	37	29	30	36	29	32	31	33	30	29	29	33	29	30	33
mean	36	31	32	35	29	43	32	31	32	31	30	32	31	30	32
%RSD	8.1	5.3	7.3	11.4	3.5	24.5	5.4	6.4	2.5	4.5	4.8	4.4	3.9	3.5	3.0

(A14768.[3]) Four outlier commercial tablets found in only two batches (highlighted) behaved far different than the others, and far different than most tablets in their own lots. (A14751-52.) Indeed, these anomalies are clear from the individual frequency of coated dissolution at 90 minutes (with the claimed release amount in red):

[3] VB Stands for validation batch, COM stands for commercial batch. (A1171:9-11.)



(A14753 (color added).) The vast majority of coated tablets measured released much less than "about 50%" of their tranexamic acid after 90 minutes using the USP Water Test.

Ferring did its own testing as well, but its testing did not follow the USP Water Test testing criteria, and is not reliable. (A1180; A1193; A1197-99; A13622-28; A13494-50; A1197; A14769; A2189:21-23.) Ferring only tested two samples per batch when the USP 27 Apparatus Type II Paddle Method requires six. (A13622-628; A13638-83; A14769.) Ferring also improperly used "lobster trap" sinkers for some tests and not others. (A1194:11-1198:20.) Further, even with this unreliability, Ferring's testing showed what Watson's did—the vast

majorities of tablets behave similarly and are far outside the patent claims. (A14769; A2189:21-23.)

Watson's ANDA contains no specification that addresses the manner in which the product dissolves in water. (A1598:15-22; A2080:15-25.) As a result, Ferring argued that the *hardness* of Watson's immediate release core portion dictated the manner in which Watson's product would dissolve in water, because there is a specification in Watson's ANDA for the hardness of its cores. Ferring alleged that tablets made with a core hardness of 17kp or above would infringe, relying on a pre-ANDA development document that was created before Watson's final (or initial) ANDA specifications were set. (A1139:20-1141:6; A991-93; A2003-06.)

B. The court found infringement for tablets with core hardness of 17 kp and greater.

During the bench trial, the district court struggled with the standard for infringement under 271(e). The court held during trial that, as a matter of law, all minor amendments made throughout the ANDA process would not be considered. (A2316; A2249-50; A2255-56.) All of Watson's amendments, including its request for final approval to the FDA (as is required by the regulations), were "minor amendments." (A1200; A1435-37; A1458-49; A1635.) The final request included Watson's final commercial scale manufacturing specifications that require Watson to manufacture its commercial product with a hardness level below

17kp, with additional processing parameters. (A13920; A1434-57.) The final request for approval also included Watson's final specifications for the thickness and uniformity of its coating. (A1466-68; A14567; 14569; A14576; A13920-67.) Because the district court considered filing of an ANDA to be an act of infringement, it refused to consider these final manufacturing specifications in its infringement analysis. (A2316.)

Prior to trial, the district court construed "modified release material" to mean "a material that modifies the release of the active pharmaceutical ingredient." (A195-96.) The court appeared to reconsider the construction of "modified release material" during trial, suggesting that "modified" could mean changing behavior *compared to the active ingredient in water*. (A2198; *see also* A1771-73; A886; A1908-09.) This is what Ferring argued in its closing. (A2197 ("And the evidence at trial showed that all the ingredients working together delay the release of the product as opposed to a powder formulation and thus modifying the release within the broad construction your Honor has proposed for us."); *see also* A1918:14-17.) In such a case, every single tablet, pill, or dosage form with an inactive ingredient that changes the manner in which tranexamic acid powder behaves in water would qualify as having a "modified release material."

At the close trial, the court orally issued tentative findings. The court tentatively found that the patents-in-suit were valid and there was infringement

under both section 271(a) and 271(e). (A2307-11.) The court also indicated, tentatively, that it would enter an injunction. (A2312-15.) The court, however, suggested that based on its finding that core or commercial products with core hardness of 17kp or more infringe, Watson could avoid infringement by submitting a change with the FDA. (A2317:1-3 ("It looks like, if you avoid or can get away from the 17 Kp, even as low as 16 with a mandatory, you're probably okay.").)

Ferring argued for the first time after the close of evidence, when the district court suggested it might issue an injunction, that it was being "substantially" harmed. (A2312-13.) Ferring did not submit any evidence of harm, whether substantial or irreparable, either during trial or during post-trial briefing.

C. After trial the court issued judgment and injunctions.

Consistent with the court's suggestion, on February 11, 2014, Watson filed an amendment to its ANDA with the FDA, further narrowing its specification to require a hardness range of 13 to 16.5kp. (A243-46.) The FDA approved that change on March 3, 2014. (A255-57.) Watson submitted these documents to the district court, explaining that Watson's ANDA (as amended) does not permit Watson to manufacture a core with a hardness above 16.5kp. (A247-51; A285-86.) Thus, Watson explained, even under the court's reasoning that hardness at 17kp or above could be infringement, its ANDA did not allow for infringement. Watson also argued that the entry of any injunction without considering the four factors set

forth in *eBay* would be in error, and submitted declarations of Napoleon Clark and Dr. David Blackburn demonstrating irreparable harm to Watson should an injunction issue. (*See* Case No. 2014-1416, Doc. No. 20 at 3-4 and Doc. No. 21 at 3-4.)

The district court denied Watson's motions. (A298-300; A320-24.) The court refused to consider the question of irreparable harm, or the approved submission to the FDA that it had previously encouraged. (A287-90.) On March 24, 2014, the court issued a written order denying Watson's request for stay. (A320-24.) The court issued a final judgment on April 14, 2014, that included a permanent injunction under 35 U.S.C. § 271(a) and § 271(e) and reset the effective date of the FDA's approval for Watson to market its generic tranexamic acid product under 35 U.S.C. § 271(e)(4)(A). (A325-27.) The court has not yet issued separate findings of fact and conclusions of law, but did suggest at the final hearing that all of its findings could be found in the trial record. (A2189:15-20; A297.)

On the same day Watson received the court's judgment, it filed a notice of appeal, and then brought a motion for stay pending appeal before this Court. (A328-30.) This Court granted that stay request pending appeal. (Doc. No. 22.)

SUMMARY OF THE ARGUMENT

The district court's findings are based upon a cascade of errors. Watson's accused products do not have the amount of "modified release material" required by the patent claims. The core portion of Watson's accused product does not have a "modified release material"—it dissolves immediately in water. Its dissolution is even faster than what the patents-in-suit describe as "immediate release tablets."

As for the finished, coated product, even assuming every ingredient included in the coating of the commercial product is a "modified release material," the total amount included in each of Watson's coated products—2.9% by weight of the tablet—is well below the amount of "modified release material" required by the patent claims.

Further, Watson's accused products do not meet the claimed dissolution profile in water when measured according to the USP Water Test (a recited element of every asserted claim). Watson's cores dissolve much faster than the claimed "modified" dissolution profile. Watson's finished coated commercial tablets are coated with a pH-dependent coating that resists dissolution in water, and dissolve far slower than the claimed "modified" dissolution profile.

The district court's decision that both the immediate release cores and commercial products with core hardness of 17kp or greater infringed under both 271(a) and 271(e) can only be based on a misapplication of the claim

construction—or application of another claim construction entirely—and a fundamental misunderstanding of the law as it applies to ANDA cases. Most importantly, Watson's ANDA as approved and as it exists today *does not allow Watson to produce products with core hardness of 17kp or greater*. Furthermore, as all experts agreed, even without any amendments to its ANDA being considered, there is no evidence that any commercial product was ever made or sold with a core hardness of 17kp.

The district court's error in its 271(e) analysis was its conclusion that the mere filing of an ANDA is an act of infringement. While filing an ANDA is indeed an "artificial" act of infringement for purposes of jurisdiction, it is still necessary to evaluate the ANDA as filed, amended, and approved to evaluate whether the product that will likely be sold infringes or not.

The district court's second error was precipitated by its first—the court refused to consider "minor amendments" in the ANDA process. That too was error. The district court's third error related to the first two. The ANDA was silent as to the issues of infringement in this case—namely, whether Watson's accused products meet the claimed dissolution profile in water when measured according to the USP Water Test. The court accepted Ferring's argument that Watson's ANDA's silence meant it allowed for infringement. This too was error, as it shifts the burden of proof to the ANDA applicant to disprove infringement.

Compounding its errors, the district court enjoined Watson's products—even products the court found do not infringe—under both 271(a) and 271(e) and issued a resetting order mandating the FDA remove Watson's approval to sell its product. Again, though, the court's finding of infringement—which is incorrect—still only relates to the hardness of the cores and assumes that a core hardness of 17kp or greater will necessarily produce a tablet that meets the claimed dissolution profile. However, Watson's ANDA *does not allow it to sell* tablets with core hardness of 17kp or greater. There is no reason to enjoin what is, even under the district court's erroneous decision, not infringing.

Further, if the claims are anywhere near as broad as Ferring suggests, they are unquestionably invalid in view of the prior art.

The bottom line here is that Watson does not *want* to make a product that meets the *in vitro* water dissolution profile of Ferring's patents, nor does Watson need to make such a product. Watson receives no benefit from any alleged accidental infringement of Ferring's patents. Modified *in vitro* dissolution in water simply has no value to any patient.

On the other hand, Watson's separately-patented commercial products have a pH-dependent coating that does not readily dissolve in water (i.e. the mouth, esophagus), but quickly dissolves in an acidic environment (i.e. the stomach) to rapidly release the active ingredient of tranexamic acid. This structure has a

benefit to patients, is separately patented over Ferring's patents, and completely avoids the narrow and valueless claims in suit.

ARGUMENT

I. Standard of review.

Claim construction is reviewed de novo. *Lighting Ballast Control v. Philips*, 744 F.3d 1272 (Fed. Cir. 2014). A district court's infringement finding after a bench trial is reviewed for clear error. *Alza v. Mylan Labs.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006). Applying an incorrect claim construction is a reversible error. *See Versa v. Ag-Bag*, 392 F.3d 1325, 1331 (Fed. Cir. 2004).

A district court's evaluation of the legal standard for infringement under section 271(a) or 271(e) is reviewed de novo. *Bradley v. Secretary of Health and Human Servs.*, 991 F.2d 1570, 1574 n.3 (Fed. Cir. 1993).

While a district court's decision to grant or deny injunctive relief is reviewed for an abuse of discretion, this Court "may find an abuse of discretion on a showing that the court made a clear error of judgment in weighing relevant factors or exercised its discretion based upon an error of law or clearly erroneous factual findings." *Innogenetics v. Abbott Labs.*, 512 F.3d 1363, 1379 (Fed. Cir. 2008).

Obviousness under 35 U.S.C. §103 is a question of law based on underlying findings of fact. *Soverain Software v. Newegg*, 705 F.3d 1333, 1336 (Fed. Cir. 2013). The underlying factual inquiries are: (1) the scope and content of the prior art, (2) the difference between the prior art and the claimed invention, (3) the level

of ordinary skill in the art, and (4) objective considerations. *Id.* The question of obviousness is decided de novo. *Id*.

II. There is no infringement.

The patent system encourages designing around patents. *Westvaco Corp. v. Int'l Paper*, 991 F.2d 735, 745 (Fed. Cir. 1993); *State Indus., Inc. v. A. O. Smith Corp.*, 751 F.2d 1226, 1235-36 (Fed. Cir. 1985). That an accused product is bioequivalent to a product allegedly covered by a patent-at-issue is irrelevant to the issue of infringement. *See Johns Hopkins Univ. v. Datascope Corp.*, 543 F.3d 1342, 1349 n.3 (Fed. Cir. 2008).

Watson's accused products do not infringe under either section 271(a) or section 271(e). They do not have the claimed amount of "modified release material" and do not meet the water dissolution profile measured by the USP Water Test.

A. The district court erred by reading out the requirement for a "modified release material."

1. The immediate release cores of Watson's accused product do not have any material that modifies the release of the active pharmaceutical ingredient.

As an initial matter, the district court's finding of infringement under section 271(e) relating to the cores is clear error because when an ANDA product is approved and sold, only the commercial ANDA product is relevant to the analysis.

Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1569 (Fed. Cir. 1997). (A1121:9-1122:1; A1676:22-1677:4.)

Each of the asserted claims requires that the accused product contain a certain amount of "modified release material." (A2831; A2880-81; A2913.) That amount ranges from about 5 to about 50% by weight in the '795 patent to about 10 to about 35% by weight in the '106 and '739 patents. (*Id.*) A "modified release material" as interpreted by the district court is "a material that modifies the release of the active pharmaceutical ingredient." (A195-96.) Watson's cores do not contain any "modified release material" required by the patent claims because there is nothing that modifies the release of the active pharmaceutical ingredient—the cores are immediate release.

The patents define an "immediate release oral dosage form" as one that "releases all of active ingredient (e.g., tranexamic acid) included therein within about 45 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method". (*See* A2853, 14:14-20; *see also* A2863, col. 34 Table 9.) They further explain that a "modified release oral dosage form" is one that releases the active ingredient "slower than an immediate release oral dosage form" when measured by the USP water test. (A2853, 14:21-27.)

Ferring's expert Dr. Williams acknowledged that if a formulation is an immediate release dosage form, "all the materials are functioning as immediate

release. They're not, either individually or together, working to change the release or modify the release." (A1144:18-1146:2; A1147:12-18.) The cores of Watson's accused products release approximately all the tranexamic acid in water within about 45 minutes—faster than tablets the patents-in-suit define as "immediate release." (A1205; A1684; A14216-33; A14259-89; *see also* A14762-67; A14754; A14731.)

Ferring's infringement expert Dr. Williams admitted that it is necessary to actually *measure* whether the ingredients modify the release of the active ingredient in order to evaluate whether they are "modified release materials":

> Q Okay. And the same material under some conditions could be an immediate release material and, under other conditions, could be a modified release material; is that right?
>
> A Some could, that's true.
>
> Q Okay. What kind of test would you have to do to determine that?
>
> A Well, one test is a dissolution test to determine. That's probably the test that most skilled persons would use.

(A1151:24-1152:6; *see also* A1151 (Williams: "Well, you have to look at how the material is acting under the conditions it's been made in order to understand how the materials are acting alone and in combination with the other excipients that are present."); A1260-61 (Williams: "One of skill in the art would have to have a test like a dissolution test to see if the release of drug has actually been modified.").)

He also confirmed that, based on the testing, the cores "appear *not* to have a modified release profile." (A1149:2-5 (emphasis added); *see also* A1150:10-22.) Dr. Maurin, Watson's expert, agreed. (A1684:6-1686:10.) Dr. Williams further confirmed that the materials in the cores *do not modify the release* of tranexamic acid:

> Q Okay. So to conclude then, none of these materials that we're looking at right now at 45 minutes, none of them contain 5 to 50 percent modified release material; is that right?
>
> A So as I stated, this composition, how they were made, these materials, in my opinion, are not functioning as a -- to modify the release of tranexamic acid --
>
> Q Okay.
>
> A -- under these conditions.
>
> Q Okay. Do they have 5 to 50 percent modified release material in them?
>
> A Under these conditions they would not.

(A1149-50.) There is nothing in the core that can be considered a "modified release material" because there is nothing in the core that "modifies the release of the active pharmaceutical ingredient."

2. Even if the coating of Watson's commercial product could be considered a "modified release material," it is far below the amount required by the claims.

The coating of Watson's commercial product comprises 2.9% by weight of the tablet. (A1700:14-21.) Even assuming every bit of the coating material is a

"modified release material," that leaves 97.1% by weight of the coated tablet (the core) that is not, under any construction, a "modified release material." Depending on the claim, each and every patent-in-suit requires 10-35% or 5-50% of the weight of the dosage form to be a "modified release material." A finding of infringement by Watson's commercial (coated) product, which does not have the required amount of "modified release material," is in clear error.

At trial, Ferring based its infringement theory on the argument that *all* of the ingredients other than the active ingredient must modify the release of tranexamic acid, and thus *all* ingredients are "modified release materials." (A1156:25-A1157:3; *see also* A634:8-13; A641:12-19; A952:2-953:3; A1030:8-12; A648:11-17; A2197:16-19.) This argument is directly contrary to Dr. William's acknowledgement that it is not the ingredient that controls whether something is a modified release material, but whether it actually modifies the release, and that testing is required to determine whether an ingredient is a modified release material. (A1151-52.)

Ferring's argument that *all* of the ingredients of a tablet, other than the active ingredient, constitute the "modified release material" must further be rejected because such a broad reading of "modified release material" was not contemplated by the claim construction, which requires that the modified release material actually modify the release. (A195.) It was also not contemplated by the

patents-in-suit, which specifically recognize that the alleged invention may have an active ingredient, a modified release material, *and* "additional excipients." (A2903, 16:12-14; *see also* A2807, 22:57-65 ("In addition to the modified release material, the formulations of the invention may also contain suitable quantities of other materials . . . e.g. preservatives, diluents . . . binders . . . disintegrants. . . ."); A2857; A2904.) Indeed, if such a broad reading of "modified release material" were accepted, the claims would unquestionably be invalid over the plethora of prior art that disclosed tranexamic acid and other excipients, including hydroxypropylcellulose.

3. The district court's determination of infringement must have been based on legal error in applying the claim construction.

At Ferring's urging, the court construed "modified release material" to mean "material that modifies the release of the active pharmaceutical ingredient." (A195-96.) Based on this construction, as discussed above, there can be no dispute that Watson's core and coated products do not infringe.

Because the district court found infringement, it is not clear that the district court actually applied its stated claim construction of "modified release material." The only way for the district court to have found infringement by Watson's core and coated tablets would be for the court to have determined, as it suggested during trial, that a "modified release material" is, in fact, any ingredient that causes tranexamic acid to behave differently in some way than in water alone. (A1771-

73; A1885-87.) This cannot be correct, as the patents-in-suit anticipate "[a] 'modified release oral dosage form' for purposes of the present invention is an oral dosage form which releases the active ingredient . . . in a manner that is slower than an immediate release oral dosage form . . . ." (A2853, 14:21-27.) Further, using this definition, literally every ingredient in a dosage form other than tranexamic acid would qualify as a "modified release material" and the patents-in-suit would unquestionably be invalid.

4. Ferring's attempt to argue new infringement theories on appeal must be rejected.

In opposition to Watson's request for a stay, Ferring abandoned the suggestion that all ingredients are the "modified release material" and suggested that the single ingredient of "hypromellose" is the "modified release material." (Case No. 2014-1416, Doc. Nos. 12-13.) This new argument is inconsistent with Ferring's litigation theory of infringement that *all* ingredients other than the active ingredient are modified release materials. (A1156:25-1157:3; *see also* A634:8-13; A641:12-19; A952:2-953:3; A1030:8-12; A648:11-17; A2197:16-19.)

Not only was that argument not one that Ferring based its infringement claims on before the district court, but it cannot support the court's finding for the first time on appeal. Among other issues, Watson's final accused products contain less than 7% hypromellose. (A13977.) Thus, it certainly is not the basis for the district court's determination that the claims of the '739 and '106 patents—both of

which require a minimum of about 10% of a modified release material—are infringed, and cannot support such a finding for the first time on appeal. (A2831; A2880-81.) Further, the grade of hypromellose used by Watson, the manner in which it is mixed within Watson's core, and the unrebutted testing done on all of Watson's uncoated tablets establishes that it does not function as a "modified release material" in Watson's product.[4] (A1584:8-1586:13; A14055-70; A1149-50.)

5. Ferring did not advance an equivalents argument.

There is also no infringement under the doctrine of equivalents because Ferring did not argue any equivalents theory relating to modified release material.

B. The district court erred in finding infringement for products that unquestionably do not meet the claimed dissolution profile in water as measured by the USP Water Test.

Separate from the fact that Watson's accused products do not have the claimed amount of modified release material, they also do not meet the claimed dissolution profile in water as measured by the USP Water Test. Watson's two-portion, two-formulation commercial ANDA product does not meet the claimed dissolution profile in water because its pH-dependent coating dissolves far slower in water than set forth in the claims. Likewise, the cores do not meet the

[4] As the *Handbook of Pharmaceutical Excipients* (incorporated by reference in the patents-in-suit) recognizes, at small amounts hypromellose can be used as a binder, while high viscosity grades can be used as release modifiers at larger amounts. (A2807-08, col. 22-23; A14535; *see also* A1159:22-1160:1; A1794:24-1795:14.)

dissolution profile because they dissolve far faster in water than claimed—they are immediate release formulations.

Of the hundreds of coated commercial products that were credibly tested by validated and reliable labs, four individual coated tablets released slightly more than 50% of their tranexamic acid at 90 minutes. (A14762-69.) Total and complete reliance on a few individual outlier tablets that behave far differently than practically every other tablet does not prove infringement by a preponderance of the evidence and, as discussed below, certainly does not support an injunction entirely barring indisputably noninfringing products. This is particularly true in this case because the USP Water Test anticipates that six tablets should be tested for reliability. When this is done, there is no infringement.

1. Watson's ANDA does not have any specification for water dissolution, and silence does not mean that it "permits" infringement.

The plaintiff must show not simply that the ANDA specification "permits" the defendant to sell or that the defendant might sell an infringing product. *Pfizer Inc. v. Teva Pharms.*, 882 F. Supp. 2d 643, 710-11 (D. Del. 2012) (citing *Glaxo,* 110 F.3d at 1570). Instead, the plaintiff must show that the product the defendant "ultimately would put on the market would likely infringe." *Id.*

Watson's ANDA does not provide any evidence to determine if Watson's commercial product will infringe because there is no specification in Watson's

ANDA that calls for measuring dissolution of its product in water. Before the district court, Ferring argued there was infringement under section 271(e) because the ANDA did not *prohibit* infringement, relying on this Court's decision in *Sunovion.* (*See* A2209:24-2210:19; A2281:21-25.) *Sunovion* does not apply here because, unlike *Sunovion*, Watson's ANDA does not have a specification relevant to the water dissolution limitations. (A1203:3-5.) *See Alcon Research v. Barr Labs.*, Nos. 12-1340, 12-1341, 2014 U.S. App. LEXIS 5023, at *11 (Fed. Cir. Mar. 18, 2014) (explaining the determination of 271(e) infringement "is based on consideration of all of the relevant evidence and, '[b]ecause drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry.'" (quotation omitted, citing *Sunovion*)). The ANDA in *Sunovion* "directly address[ed] the infringement question," because the patent claims were directed to the amount of a particular isomer present in the accused product. *Sunovion Pharms. v. Teva Pharms.*, 731 F.3d 1271, 1278 (Fed. Cir. 2013).

2. The district court's 271(e) legal analysis was in error because it refused to consider the ANDA in its entirety.

It is well-settled that "[t]he patentee's burden of proving ultimate infringement [under section 271(e)] is *not met by the filing of the ANDA*". *Glaxo v.*

Novopharm, 110 F.3d 1562, 70 (Fed. Cir. 1997) (emphasis added). An ANDA filing is merely an artificial act of infringement that creates case-or-controversy jurisdiction. *Pozen v. Par Pharmaceutical*, 696 F.3d 1151, 1157 n.2 (Fed. Cir. 2012). Rather, "[w]hat is likely to be sold, or, preferably, what will be sold, will ultimately determine whether infringement exists." *Glaxo*, 110 F.3d at 1570. Thus, *all* materials should be considered. *Alcon*, 2014 U.S. App. LEXIS 5023, at *11-15; *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1248-49 (Fed. Cir. 2000); *Glaxo v. Novopharm*, 931 F. Supp. 1280, 1285-89 (E.D.N.C. 1996), *aff'd*, 110 F.3d 1562, 1567-70 (Fed. Cir. 1997).

The district court erred in its literal reading of section 271(e) to mean that filing an ANDA, by itself, establishes infringement. (A2248:19-25; A2249:17-2250:23.) This in turn led to the district court's erroneous interpretation of 271(e) to preclude from consideration any ANDA specification changes made as "minor amendments" as the ANDA was pending before the FDA. (A2248:19-2256:15; *see also* A2192:22-2193:2; A2316.) There is no legal basis for the district court's ruling that the "minor amendments" should be excluded from the infringement analysis. *All* materials Watson submitted to the FDA during the ANDA process—including scale-up processing parameters and all amendments to its batch records—must be considered, because they define what is to be (and what has been) marketed and sold. *Glaxo*, 110 F.3d at 1570; *Glaxo,* 931 F. Supp. at 1289.

The district found infringement for products with cores of 17kp hardness or greater because the court refused to consider the 16kp turn-back and the fact that based on the specifications, there was no evidence Watson ever made or sold a tablet with a 17kp core. (A2256:11-15; A2317.) When all materials are considered (including all amendments), there is no support for the court's finding that Watson's product infringes under 271(e) because the undisputed and admitted evidence is that Watson did not, and will not, make, use, or sell a product with a 17kp core under the amended specifications of its FDA-approved ANDA. (A14186; A14567; A14569; A1408; A1435; A1464.)

3. The court erred in its determination that products with core hardness of 17kp and greater met the claimed dissolution profile in water based solely on PTX381.

It is well-settled that pre-submission data or withdrawn or superseded specifications are irrelevant. *Glaxo v. Novopharm*, 931 F. Supp. 1280, 1289 (E.D.N.C. 1996), *aff'd*, 110 F.3d 1562 (Fed. Cir. 1997).

The only evidence Ferring presented relating to infringement at a hardness of 17kp was a single archived project document on experimental cores during development of Watson's ANDA. (A991:6-993:5; A1622:14-1625:7; A2070-72; A1617-19; A14840-47.) These experimental cores were made before any patent-in-suit issued, were not made pursuant to the final ANDA specifications, and were well within the safe harbor afforded generic pharmaceutical companies by section

271(e)(1) for developmental work done to support an ANDA application. (A1618; A2783.)

This pre-ANDA document is legally irrelevant to the question of 271(a) or 271(e) infringement. PTX381 is not part of the ANDA, either as filed or as finally approved, and has nothing to do with either Watson's ANDA product as approved or its products as eventually sold. *Glaxo,* 931 F. Supp. at 1289; *see also Glaxo*, 110 F.3d at 1570; *Alcon*, 2014 U.S. App. LEXIS 5023, at *10-14. Indeed, when the entire ANDA is considered, PTX381 has no relevance because all experts agreed that Watson's ANDA includes a specification that requires the hardness to be turned back if it reaches 16kp, and there was no evidence any commercial product was ever made at 17kp. (A14186; A1149; A1444; A1465; A14567; A1649-50.)

This pre-scale-up document is also factually irrelevant to the question of 271(a) and 271(e) infringement. PTX381 was created before scale-up. Both parties' experts agreed that the scale-up activities could have affected dissolution, and the only way to know would be to test the dosage forms both before and after those scale-up activities occurred. (A1201:3-1205:11; A1622:14-1625:7; A1635:2-1647:10; A1139-40.) When that was done, there was no evidence either of any 17kp core or of any core acting in any other way than immediate release. (A1205:1-16.)

4. A few commercial product outliers do not prove infringement under either 271(a) or 271(e).

The independent claims of the '106 and '795 patents require "not less than about 50% by weight of the tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes." (A2880-81; A2913.) The '739 patent requires "about 100% by weight tranexamic acid or pharmaceutically acceptable salt thereof released by about 120 minutes." (A2831.)

There is no dispute that the vast majority of the tested accused products did not meet these release rates. This is because Watson's functional pH-dependent coated final ANDA product resists dissolution in water and dissolves far *slower* than the dissolution rate claimed by the patents-in-suit. (A14216-33; A14259-89; A13793-861.) Likewise, not a single core that was tested met the claimed dissolution profile in water. This is because Watson's core is immediate release and dissolves far *faster* than the dissolution rate claimed by the patents-in-suit. Ferring based its infringement arguments on a few coated outliers. (A1001:11-1007-12.) As discussed below, outliers do not prove infringement.

a. As a general matter, outliers do not have the reliability to prove infringement.

Reliance on outliers does not prove infringement by a preponderance of the evidence. Testing must have the "reliability and consistency to support a finding by a preponderance." *Eastman Kodak Co. v. Agfa-Gevaert N.V.,* 560 F. Supp. 2d

227, 277-79 (W.D.N.Y. 2007), *adopted*, 560 F. Supp. 2d 227 (W.D.N.Y. 2008), *aff'd*, 351 Fed. Appx. 441 (Fed. Cir. 2009); *see also Astra Aktiebolag v. Andrx Pharms.*, 222 F. Supp. 2d 423, 521-22 (S.D.N.Y. 2002), *aff'd*, *In re Omperazole Patent Litig.*, 84 Fed. Appx. 76 (Fed. Cir. 2003). Variability in test results and a "high percentage of non-infringing samples lessens to insignificance any confidence about the accuracy of the would-be infringing sample." *Eastman,* 560 F. Supp. 2d at 277-79.

The outliers are not representative of Watson's final ANDA product. (A1694:6-A1695:2.) Indeed, Dr. Maurin, who oversaw the testing and specifically observed the dissolution tests of the outliers found only in two batches, testified "there was something incomplete about the coating. It lacked coating integrity. The coating on the tablet sort of came apart and opened up. It was very atypical and aberrant relative to all the other 176 tablets that were examined." (A1694-95.) Watson does not intend to make a product that meets Ferring's claimed dissolution profile in water, and for the vast majority of its products succeeds.

Watson and its independent lab AAI Pharma tested over 350 coated tablets and cores, properly following the USP and testing 6 tablets per lot. (A14216-33; A14259-89; A1658:14-1660:13; A14751-54; A14762; A14764; A14766; A14768.) The extremely high percentage of individual samples that do not meet the dissolution profile (354/360) lessens to insignificance any confidence about the

accuracy of the would-be infringing samples. Indeed, the rarity of the outliers and their extreme dissimilarity from the vast majority of the other samples and batches tested merely demonstrates that they do not reliably represent Watson's final ANDA product.

Ferring's own purported testing cannot support an infringement finding. First, Ferring's testing was completely unreliable. (A13622-28; A13693-715; A13494-501; A13689-92; A14769; A1197-200; A1179:10-1180:3; A1186:3-14; A1179-80; A1185-86; A13622-28.) The district court correctly found the outlier results from Pharmatek was "just way off the map" and excluded it. (A2189:21-23.) Further, no individual core sample fell within the claimed dissolution range. (A13419-64; A13638-83.)

b. Specific to this case, the outliers do not meet the criteria set forth in the USP Water Test.

Each and every claim requires that the "formulation provides an in-vitro dissolution release rate of the tranexamic acid or pharmaceutically acceptable salt thereof, when measured by the USP 27 Apparatus Type II Paddle Method". (A2831; A2880-82; A2913.) USP 27 Chapter 711 describes the *method* for conducting a scientifically valid measurement, using a USP 27 Apparatus Type II. (A13380-81; *see also* A853:14-855:9; A1126:16-1127:19; A1131:6-1132:4; A1162:2-18; A1164:7-25; A1167:23-1168:2.) The USP 27 Chapter 711 requires at least six tablets from a lot or batch be tested in water:

Interpretation—

Unit Sample—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to the accompanying Acceptance Table. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content; the 5%, 15%, and 25% values in the *Acceptance Table* are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than $Q + 5\%$.
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q, and no unit is less than $Q - 15\%$.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, not more than 2 units are less than $Q - 15\%$, and no unit is less than $Q - 25\%$.

(A13381 (emphasis added).)

That the USP Water Test requires testing of six tablets is further supported by the fact that the patent specification and prosecution history repeatedly include testing on at least six samples when disclosing the dissolution characteristics of each and every formulation described (including the prior art):

Example 4a

Comparative Example

In Comparative Example 4A, a 500 mg immediate release tranexamic acid tablet, approved and marketed in Canada under the name Cyklokapron was obtained and dissolution tested under USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. The dissolution results are listed in Table 10A below:

TABLE 10A

Sample #	% dissolved in 15 min.	% dissolved in 30 min.	% dissolve in 45 min.	% dissolved in 60 min.
1	102	104	105	106
2	102	104	105	106
3	101	102	102	105
4	99	101	102	103
5	100	102	103	104
6	99	101	102	104
Average	101	102	103	105
% RSD	1.4	1.3	1.4	1.1

(A2814 (emphasis added); *see also* A2813, Tables 9 and 10; A2863, Tables 9, 10 and 10A; A2907, Table 10A.) Dr. Williams confirmed he tested six tablets and that his USP Type II dissolution testing apparatus—a VanKel VK 6010 dissolution tester—holds six testing vessels. (A1127:20-1128:23; A14630.)

Applying the acceptance criteria of the USP Water Test, which requires all six samples in a test to be within the dissolution profile, not one batch tested by any lab infringes. (A1177:10-17; A1179:4-1180:24; A1659:3-1660:12; A1679:9-19; A1690:2-13; A1691:8-22.) Watson and AAI Pharma performed dissolution tests from samples taken from three validation lots and twelve commercial lots on both coated tablets and cores. (A14216-33; A14259-89.) Each time, six tablets from each batch were tested. (*Id.*; A1658:14-1660:13.) Using the acceptance criteria in the USP, not one batch met the dissolution profile required by the

claims. (A1170-83; A1687-94; A1697.) The testing performed by Ferring—which was apparently created to find outliers—did not follow the claimed USP Water Test. (A1165:2-17; A1170:10-20; A1180; A1193; A1197-99; A13494-501; A13626-28.) The court tentatively ruled that the USP Water Test requires six samples for 271(e) infringement but not 271(a) infringement, but the court's final decision on the issue is not entirely clear. (A2189:24-2191:10; A295:3-296:6.)

5. Ferring also failed to prove Watson's accused products meet the water dissolution profile limitation under the doctrine of equivalents.

Ferring did not present an argument regarding whether Watson's accused products infringe the limitation that the "formulation provides an in-vitro dissolution release rate of the tranexamic acid or pharmaceutically acceptable salt thereof, when measured by the USP 27 Apparatus Type II Paddle Method" under the doctrine of equivalents. Rather, Ferring's expert suggested that dissolution results in the simulated gastric fluid and dissolution results in pH 6.8 media "performed the same -- substantially the same release modifying function in simulated gastric fluid as in water" and provide "the same benefits as the formulations of the patents-in-suit". (A1034:13-1035:3.) Ferring offered no opinion on which claim element was missing, let alone an opinion on the insubstantiality of the differences between the missing claim element and the allegedly equivalent element. Thus, there is no support for any argument that if the

accused products do not literally infringe there is infringement under the doctrine of equivalents.

In addition, the evidence demonstrates that Watson's accused products are substantially different from the claimed invention. The core of Watson's accused product is an immediate release formulation and the coating is a pH-dependent coating. Watson's commercial ANDA product releases its tranexamic acid in a substantially different way (using an immediate release core and a pH-dependent coating) to obtain a substantially different result (different dissolution rate when measured by the USP Water Test) than the formulation claimed in the patents-in-suit. That Watson was able to obtain its own patent over the patents-in-suit further demonstrates that there is no equivalents infringement. (A14545.) *See Hoganas AB v. Dresser Indus*., 9 F.3d 948, 954 (Fed. Cir. 1993).

Not only is there no factual support for the doctrine of equivalents, there is no legal support. The claims were amended to add the exact dissolution elements Ferring now apparently seeks to avoid. (A2961; A10725-39; A9193-99.) Ferring cannot now attempt to use the dissolution profile in an entirely different medium (acidic simulated gastric fluid) to recapture subject matter surrendered to acquire the patent. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 734 (2002).

C. The dependent claims are also not infringed.

If an independent claim is not infringed, then each of the corresponding dependent claims cannot be infringed. *Becton Dickinson & Co. v. C.R. Bard, Inc.*, 922 F.2d 792, 798 (Fed. Cir. 1990). Because the independent claims are not infringed, the dependent claims are also not infringed.

D. Even if the district court were correct that tablets with core hardness of 17kp or greater infringed, there still is no infringement in this case because Watson's ANDA does not permit core hardness of 17kp or greater and there is no evidence any commercial product was ever sold with core hardness of 17kp or greater.

Watson does not manufacture or sell tablets with a hardness of 17kp or greater, and there is no evidence to the contrary. (A2077:1-25; A1149.) Thus, even under the court's decision that tablets with core hardness of greater than 17kp infringe, there is no evidence of any infringement under section 271(a).

Further, Watson's ANDA, as amended before approval, did not permit tablets with hardness above 17kp. (A13920.) Watson's approved ANDA specifications included an explicit instruction to monitor the manufacture of the core tablets with a 16kp "alert limit," which instructed the operators of the compression machine to maintain core tablet hardness well below 17kp. (A14567; A14569; A14577.) There was no evidence that an FDA-approved commercial tablet with a hardness of 17kp was ever made, or sold, by Watson. And, after the amendment suggested by the district court at the close of trial, Watson's ANDA

now only permits it to make, use, and sell tablets with cores that have a hardness of 13-16.5kp. (A243-46; A255-57.)

Thus, even under the court's decision that tablets with core hardness of greater than 17kp infringe, there is no evidence of any infringement under section 271(a) or 271(e).

III. Separate from the question of infringement, the injunction and resetting order injunction cannot stand.

Injunctive relief is an "extraordinary remedy." *Weinberger v. Romero-Barcelo*, 456 U.S. 305, 312 (1982). The Supreme Court in *eBay* unequivocally rejected the "general rule that courts will issue permanent injunctions against patent infringement absent exceptional circumstances." *eBay v. MercExchange*, 547 U.S. 388, 391-92 (2006). The Supreme Court counseled that "[a]ccording to well-established principles of equity, a plaintiff seeking a permanent injunction must satisfy a four-factor test before a court may grant such relief." *Id.* at 391. This test requires plaintiff to show: (1) irreparable injury; (2) monetary damages are inadequate; (3) considering the balance of hardships between a remedy in equity is warranted; and (4) the public interest would not be disserved. *Id.* As this Court counseled in *Ecolab v. FMC*, a district court that fails "to consider any of the *eBay* factors and failed to make any factual findings regarding those factors" commits an abuse of discretion. 569 F.3d 1335, 1352 (Fed. Cir. 2008).

A. The injunction must be vacated because it violates *eBay*.

The district court's injunction under sections 271(a) and 271(e) should be vacated because it is premised upon the long-overruled presumption that a patent owner is irreparably harmed upon a finding of infringement. At the close of trial, the court presumed an injunction would issue—even though Ferring never made a showing and the district court never made a finding on any of the *eBay* factors. (A2310:25-2311:1.) Indeed, on post-trial motion practice, the court *explicitly* refused to consider the question of irreparable harm—whether incurred by Ferring or Watson. (A287-90.)

The district court's decision to enter an injunction without considering a single *eBay* factor was plainly in error. Here, the district court did not merely make "an error of judgment in weighing relevant factors"—the court refused to consider the factors at all. Ferring (the party with the burden of showing entitlement to injunctive relief) submitted *no evidence whatsoever* that irreparable harm had been caused by Watson's competition in this market. (A289-90.) Instead, Ferring's only claim of harm was conclusory attorney argument, made well after the close of evidence. (A2312-13.) The district court accepted this naked representation as fact, and presumed irreparable harm without any analysis at all. As this Court counseled in *Ecolab*, the failure to consider the *eBay* factors is an abuse of discretion. The injunction should be vacated.

B. The injunction is in error because it applies to products that even the district court found were not infringing.

Courts have recognized that injunctions should not be so broad as to enjoin a competitor for making, using, and selling products that do not infringe. *See Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1366 (Fed. Cir. 1998); *Joy Techs., Inc. v. Flakt, Inc.*, 6 F.3d 770, 777 (Fed. Cir. 1993). This rule applies here as there is no dispute that the injunction bars Watson from selling noninfringing products.

The district court found that Watson's accused products do not infringe at a core hardness level less than 17kp. (A2317.) There is no evidence—not one iota—that any commercial product was manufactured by Watson at a 17kp hardness, because the ANDA as approved included a turn-back that should not have allowed tablets with a hardness of 17kp. (A2075:44-20; A1149:18-23; A14567; A14569; A14576.) Even Ferring's expert admitted that all tested products manufactured by Watson fell below 17kp. (A2075:14-20; A1149:18-23.) Further, there is no dispute that Watson's ANDA as amended pursuant to the court's instructions does not allow for core hardness of 17kp. (A243-46; A255-57.) An injunction enjoining products even the district court found do not infringe is improper.

C. The resetting order injunction cannot stand because it applies to noninfringing products; contrary to Ferring's arguments, there must be discretion in deciding whether to issue a resetting order injunction.

A resetting order is an injunction by a different name. *See Carson v. Am. Brands, Inc.,* 450 U.S. 79, 83-89 (1981) (explaining the "practical effect" of the lower court's decision is an injunction because it "would have permanently enjoined" certain activities); *SmithKline Beecham Corp. v. Apotex Corp.*, 247 F. Supp. 2d 1011, 1050 (N.D. Ill. 2003) ("Section 271(e)(4)(A) is an amendment to the patent statute and it provides relief in the nature of an injunction, for an injunction is simply a court order (other than a purely procedural one) to do or not to do something."). The resetting order under section 271(e)—a *de facto* injunction—also cannot stand.

1. A resetting order injunction is not mandatory.

Ferring's argument before the district court—that the court accepted—is that a resetting order is mandatory and that there is no discretion at all, even in a case like this where it applies only to noninfringing products. That cannot be the law. The same equitable principles the *eBay* court considered must also be considered here.

Section 271(e) defines a set of potential remedies that are available for a case brought under 271(e)(2). One such remedy is to allow the court to order the FDA to set the approval date of the ANDA to that of the expiration date of the

patent-in-suit. 35 U.S.C. § 271(e)(4)(A). This is referred to as a "resetting order" injunction. While the statute uses the language "shall," at least one court directly considering the issue has concluded that a finding of infringement does not *require* the court to issue a resetting order injunction. *SmithKline*, 247 F. Supp. 2d at 1050, *aff'd,* 365 F.3d 1306 (Fed. Cir. 2004), *superseded by,* 403 F.3d 1331 (Fed. Cir. 2005).

In *SmithKline*, the court reasoned, "As a form of patent injunction, the delay order is subject to the principles that govern such injunctions . . . ." *Id.* at 1050. The court specifically addressed the "shall" language in section 271(e)(4)(a), explaining "[s]hall versus may" arguments are "weak in general" and in that case in particular. *Id.* at 1049-50 (citations omitted). On appeal, the Federal Circuit did not reach the question of whether a resetting order injunction was appropriate because it invalidated the patent-in-suit. *SmithKline*, 403 F.3d at 1335-36.

The *SmithKline* case is instructive here. Watson does not want to infringe Ferring's patents, designed around them, and obtains absolutely no benefit from any infrequent or accidental infringement to the extent that there even is any at all. In reality, the infringement finding under section 271(e) relates only to a non-existent product that could possibly, in theory, be made with a 17kp hardness core. That theoretical product is one that Watson does not want to sell—its ANDA includes a 16kp "alert limit," which mandates that the hardness of Watson's tablets

be kept below 16kp, and certainly below 17kp. (A1139.) Further, as currently amended and approved by the FDA, Watson's ANDA does not permit it to sell tablets with 17kp hardness. (A243-46; A255-57; *see also* A655:21-656:15.) Thus, there is no basis for a resetting order injunction.

Further, a resetting order injunction prohibiting Watson from selling noninfringing products is unwarranted, and certainly not what Congress intended with the Hatch-Waxman Act. Congress sought to enable lower-cost generic drugs to be marketed more quickly to provide an important benefit to the public. *Teva Pharm. v. Crawford*, 410 F.3d 51, 54 (D.C. Cir. 2005); *Eli Lilly v. Medtronic*, 496 U.S. 661, 676 (1990); *Glaxo v. Novopharm*, 110 F.3d 1562, 1568 (Fed. Cir. 1997). That goal would *not* be achieved by a resetting order injunction.

2. Changing the approval date of the ANDA would be inappropriate for at most *de minimus* acts that could only be characterized as infringement under 271(a).

Likewise, when any infringement finding is based on the commercial product as sold under 271(a), instead of the ANDA product under 271(e), a resetting order injunction is inappropriate. In *Sanofi-Aventis,* the court considered the requirements needed to issue an order changing the effective date of the ANDA to that of the patent-in-suit. *Sanofi-Aventis Deutschland Gmbh v. Glenmark Pharms. Inc., USA*, 821 F. Supp. 2d 681, 697 (D.N.J. 2011). While the case arose out of the filing of an ANDA, the plaintiff attempted to prove much of its case by

referring to acts that were other than filing the ANDA, such as selling the generic product or acts of contributory or inducing infringement. *Id.* at 694-97. In considering whether to issue an order delaying the approval date of the ANDA, the court found that because the infringing acts occurred under sub-sections of 271 other than 271(e), the remedy of changing the approval date of the ANDA was not available. *Id.* at 697.

Ferring's arguments regarding a resetting order injunction relate not to alleged infringement under section 271(e), but to the commercial product (alleged infringement under 271(a)). Ferring pointed at trial to the outliers, which relate to Watson's the commercial product—not the ANDA—to argue there was infringement. Even if true, infringement under section 271(a) would only be relevant to an injunction under section 271(a), not a resetting order injunction under 271(e). *See Sanofi-Aventis*, 821 F. Supp. 2d at 697. As such, the remedy of changing the approval date of the ANDA should not apply.

IV. The district court incorrectly concluded that 650mg in a modified release formulation was non-obvious.

The patents-in-suit are directed to 650mg of tranexamic acid to treat HMB using a range of daily dosage of 1950 or 3900mg (one or two tablets three times a day). The prior art disclosed 500mg of tranexamic acid to treat HMB using a range of daily dosage of 1500 to 4000mg (one or two tablets three to four times a day). The patents-in-suit claim to be bioequivalent to an immediate release

tranexamic acid formulation that was created to mimic the prior art. That is, the alleged invention acts the same in the body as the immediate release prior art tablets. There is no novelty here.

After trial, the district court declined to find the asserted claims invalid. The court correctly recognized "[Ferring] did not invent tranexamic acid, nor did [Ferring] invent any of these polymers that can be used to modify release, nor did [Ferring] invent a method of modifying release through use of these polymers." (A2208:3-7.) The court explained that the unique part of the invention "consists of a dosage of 650mg per tablet, 1300, in other words, approaching four grams a day in order to achieve that maximum [ ] C_{max}." (A2308:1-13; *see also* A1810:9-1813:8.) The court explained, "of course, all of that information was in the prior art and in the prior studies. But nobody produced nor studied a higher tablet." (A2309:12-14.) The court concluded:

> It's not obvious. Clearly, in the prior art, in the prior patents, everybody knew about modification techniques, knew about using polymers, long since used. That's clearly in the prior art.
>
> But the unique invention here is the combining of those two elements, the 650 higher dosage allowing for higher Cmax at the standard Tmax rates with the delay in the release of the tablet into the stomach.

(A2309:21-2310:5.)

There is nothing inventive about changing the dosage form from 500mg to 650mg. *Merck v. Biocraft*, 874 F.2d 804, 809 (Fed. Cir 1989) ("Normally, it is to be expected that a change in temperature, or concentration, or in both, would be an unpatentable modification."). A 650mg tablet is a pragmatic solution in view of the guidance set forth in the prior art, and does not introduce a point of novelty. Nor does its combination with known techniques for delaying release in the stomach that result in pharmacokinetic data that are equivalent to the immediate release formulation marketed for years introduce a point of novelty.

While the independent claims use slightly different ranges and wording, the differences between each of the independent claims are insubstantial. (A14814; A1796:9-1797:12.) Each of the elements of the asserted claims are set forth in prior art and their combination would be obvious to one of ordinary skill in the art.

A. Each element of the claims is disclosed in the prior art.

There are numerous prior art references discussing the use of tranexamic acid for HMB, including a report by the European Agency for the Evaluation of Medical Products ("CPMP"). That report evaluates the safety and effectiveness of Cyclo-f, a 500mg tranexamic acid product to treat HMB, based on decades of use of Cyklokapron, another a 500mg tranexamic acid product used for decades throughout Europe. (A13629-37.)

The CPMP describes Cyklo-f in great detail. It explains that Cyklo-f is a film-coated tablet with 500mg tranexamic acid. (A13634.) Its therapeutic indication is for treatment of "menorrhagia" (HMB). (*Id.*) The ingredients in the core are: microcrystalline cellulose, hydroxypropylcellulose, talc, magnesium stearate, colloidal anhydrous silica, and povidone. (A13636.) The ingredients in the coating are: methacrylate polymers, titanium dioxide (E171), talc, magnesium stearate, macrogel 8000, and vanillin. (A13636-37.)

The CPMP also discloses Cyklo-f's pharmacokinetic properties. For example, it defines a C_{max} of approximately 5mcg/ml following a single oral dose of 500mg and a C_{max} of approximately 15mcg/ml after a dose of 2000mg. (A13636.) It explains the bioavalability is approximately 35%. (*Id.*)

The CPMP suggested that there were no significant side effects associated with a daily dose of up to 4000mg a day. (A13631.) The report, however, did suggest that increasing the does to 6000mg a day would increase efficacy, but may also increase mild gastrointestinal side-effects. (*Id.*) The disclosure of the CPMP was consistent with other prior art. (A1753:3-1781:9; A13382-98; A12515-21; A14490-97; A11490-534; A13399-401.)

B. It would have been obvious to use 650mg of tranexamic acid.

The CPMP defined the dosage frequency and maximum dose by recommending two 500mg tablets (1000mg total) three times daily (every eight

hours) or four times daily (every six hours) for a maximum daily dose of 4000mg. (A13631; A13634; A13389.) Such a dose was thought to result in a clinically relevant reduction in menstrual blood without inducing significant adverse events. (*Id.*) The CPMP's recommendations, therefore, established a baseline dosage (two 500mg tablets), a convenient frequency (every eight hours) and maximum daily dose (4000mg). (*See also* A13385-86; A13389.)

In view of this, the choice of a 650mg dosage would have been an obvious and pragmatic choice for tablet strength. (A1787:10-1788:3.) Two 650mg tablets (1300mg) three times a day results in a daily dose of 3900mg, just below the well-recognized and accepted daily dose of 4000mg per day. It would have been an obvious design choice to minimize frequency while maintaining the daily dosage set forth in the prior art. (A1787:10-1788:3; A790:15-791:5 A1751; A1787-88.) This is particularly true given that such a dose would decrease frequency of administration, produce a more constant blood level as called for in the prior art, and address any concerns about adverse side effects. (A14480, 1:15-25.)

C. Use of modified release materials, including in combination with tranexamic acid, was well-known.

Combining modified release materials with tranexamic acid in tablets is also not novel. The prior art recognized tranexamic acid could be used as a modified formulation. (A1793:7-1794:20; A14481, 3:11-15; A14517.) Specifically, prior art U.S. Patent No. 5,858,411 describes tranexamic acid as a drug that can be used with

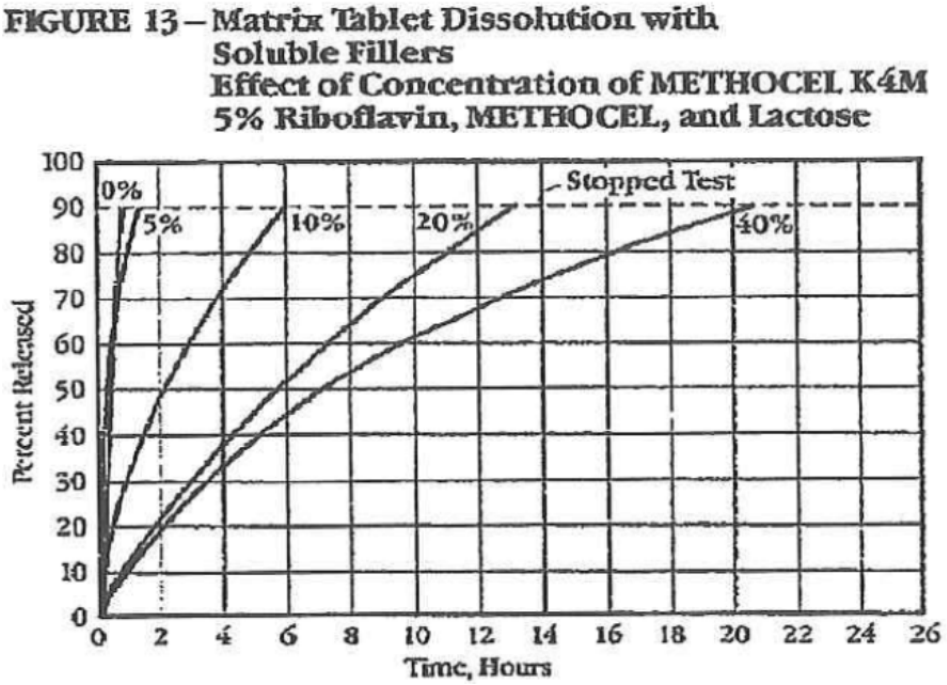
controlled-release preparations, including hydroxypropylcellulose and hydroxypropylmethylcellulose. (A14481, 3:11-15; A14482, 5:44-45.) The '411 patent also provides the motivation for using modified release materials with tranexamic acid because use of modified release materials was thought to decrease adverse side effects due to high blood levels, as well as to decrease dosage strength and frequency. (A1793:7-1794:21.)

In addition, the prior art used polymers as ingredients. The CPMP lists excipients included in Cyklo-f, including hydroxypropylcellulose. (A13636.) Watson's expert Dr. Arthur Kibbe confirmed that one of skill in the art would know hydroxypropylcellulose can be a modifier in certain conditions. (A1769:13-1771:9.) As the Handbook of Pharmaceutical Excipients (incorporated by reference into the patents-in-suit) recognizes, hydroxypropylcellulose was known to act as a modified release material to extend the release of drug products from tablet formulations when used in the range of 15-35% weight percent. (A14530; A2807-08, cols. 22-23.) There is nothing novel about using a "modified release material" within a tranexamic acid tablet.

D. The claimed *in vitro* "modified release" dissolution rates are obvious.

The claimed *in vitro* dissolution rates impart no meaningful value to this drug product. The release profile is simply a collection of observed laboratory values, resulting from the predictable and well known addition of a release modifying

polymer to the prior art formulation. Dr. Kibbe confirmed that people of skill in the art knew a modified release material can be used to alter dissolution rate using routine testing. (A1794:16-1795:14; A1797:2-12.) For example, Dow discloses that in tablet formulations, hydroxypropylcellulose can be used as a binder, a film-coating, and an *extended release material*, depending on the concentration and grade:



(A14444; *see also* A14530.) Dow demonstrates not only that the use of "modified release materials" to alter the dissolution rate was known, but that one of ordinary of ordinary skill in the art could predict the dissolution rate and time of a tablet formulation using the percentages by weight of hydroxypropylcellulose. The clinically meaningless observation of how a tablet releases an active ingredient in water, outside the body, does not constitute a patentable invention.

E. There is nothing novel about the dependent claims.

The dependent claims add additional limitations that relate to (1) the form of modified release material; (2) dosage form; (3) the percent of tranexamic acid of total tablet weight; (4) method of administration claims; and (5) mean maximum plasma concentration, time to maximum plasma concentration, or bioavailablity. (A2831-32; A2880-83; A1800:7-16; A14816-29.) None of the limitations in these claims are novel; they are obvious for the same reasons as the independent claims.

1. The dependent claims relating to the form of modified release material, dosage form, or amount of tranexamic acid are obvious for the same reasons as the independent claims.

The dependent claims relating to (1) the form of modified release material are claims 4 and 5 of the ’739 patent, claims 18, 19, 40, and 41 of the ’106 patent, and claim 10 of the ’795 patent. (A2832; A2881-82; A2913.) These dependent claims are invalid for the same reason that the respective independent claims were invalid as obvious, as the specific modified release materials claimed are disclosed in the CPMP and the ’411 patent. (A1800:18-1802:7.)

The claim relating to (2) the dosage form is claim 15 of the ’106 patent. (A2881.) This dependent claim is also invalid for the same reason that the respective independent claims were invalid as obvious. (A1803:22-1804:14.) Various dosage forms were well-known in the art. (A13629; A1803:22-1804:14; A8216-17; A8287-88.)

Dependent claims 5, 8, and 9 of the ’795 patent relate to (3) the percent of tranexamic acid of the total tablet weight. (A2881.) These claims are obvious based on the disclosure of tranexamic acid formulations rendering the independent claims invalid. (A1802:8-1803:21; A13382-98; A13629-37; A12515-21.) The percentage by weight of tranexamic acid does not render these claims non-obvious.

The dependent claims relating to (4) methods of administration are claims 30, 31, 32, 33, 34, 35, and 36 of the ’106 patent. (A2882.) Once again, these dependent claims are invalid for the same reason that the respective independent claims were invalid as obvious. (A1804:17-24.) The method of using tranexamic acid as an antifibrinolytic agent in treating HMB was well-known. (A13629-37; A13389.)

2. The pharmacokinetic properties are features of the claimed formulations and were expected from the prior art.

The dependent claims relating to (5) pharmacokinetic properties are claims 8, 9, 10, 12, and 13 of the ’739 patent, claims 5, 6, 7, 8, 16, and 37 of the ’106 patent, and claim 6 of the ’795 patent. (A2831-32; A2881; A2913; A1713:8-1720:3.) These are all just characteristics of the claimed formulation, they do not render the claims non-obvious; the pharmacokinetics of the claimed formulations were disclosed and expected from the prior art. (A1805:3-1810:6; A1813:9-1818:14.)

The prior art disclosed the pharmacokinetics of the 500mg tranexamic acid formulations:

CPMP [WTX1191]	
C_{max} increased linearly with doses between 500mg and 2000mg	
500mg C_{max}	5 mcg/ml
2000g C_{max}	15 mcg/ml
Bioavailability	35% (95% recovered)
Wellington [WTX1160]	
2000mg C_{max}	14.4 mcg/ml
Dose proportionally adjusted – 1300mg C_{max}	9.4 mcg/ml
Bioavailability	33.4-34.9%
t_{max}	2.8hrs
Pilbrant [WTX1355]	
2000mg C_{max}	14.4 mcg/ml
Dose proportionally adjusted – 1300mg C_{max}	9.4 mcg/ml
Bioavailability	33.4-34.9% in 24hrs
t_{max}	2.8-2.9hrs
Verstraete [WTX1357]	
1000mg C_{max}	8 mcg/ml
Does proportionally adjusted – 1300mg C_{max}	10.4 mcg/ml
Bioavailability	39% in 24hrs
t_{max}	3hrs
Foreign Labeling [WTX1013]	
Canadian Cyklokapron Label – Bioavailability	40%

(A14821; A1807:6-10; A13629-37; A13382-98; A14490-97; A11490-34; A14498-523.) The prior art also disclosed that C_{max} is linear. (A11503; A11508; A11585.)

With respect to the maximum plasma concentration claims (C_{max}), the prior art disclosed a C_{max} of from 9.4-10.4mcg/ml when proportionally (linearly) adjusted for the 1300mg dose—well-within the claimed ranges:

739 Patent	
Claim 8: C_{max} about 9 to about 14.5 mcg/ml (1300 mg)	Prior art disclosed dose proportionally adjusted C_{max} of 9.4-10.4 mcg/ml, within claimed range [WTX1160] [WTX1355] [WTX1357]
Claim 13: C_{max} about 9 to about 17.5 mcg/ml (1300 mg)	
106 Patent	
Claim 5: Same as 739 patent claim 8	
Claim 6: C_{max} about 5 to about 25mcg/ml (1300 mg)	
795 Patent	
Claim 6: C_{max} about 5 to about 17.5 mcg/ml (1300 mg)	

(A14822; A1809:19-1810:6; A1813:9-1814:21; A13382-98; A14490-97; A14498-523.) Likewise, Dr. Kibbe testified that the multi-dose plasma concentration claims would fall within the ranges of the prior art:

739 Patent	
Claim 9: C_{max} about 12.5 to about 25 mcg/ml (1300 mg 3x/day)	Prior art disclosed dose proportionally adjusted C_{max} of 9.4-10.4 mcg/ml; steady state levels would be within claimed range [WTX1160] [WTX1355] [WTX1357]
Claim 12: C_{max} about 10 to about 20 mcg/ml (1300 mg 3x/day)	
106 Patent	
Claim 7: Same as 739 patent claim 12	
Claim 37: Same as 739 patent claim 12	

(A14823; A1814:24-1816:13; A13382-98; A14490-97; A14498-523.)

With respect to the time to maximum plasma concentration claims (T_{max}) the prior art disclosed a T_{max} of from 2.8-3 hours, again within the claimed ranges:

739 Patent	
Claim 10: t_{max} about 2 hours to about 3.5 (650mg)	Prior art disclosed t_{max} of approximately 2.8-3hrs, within claimed range [WTX1160] [WTX1355] [WTX1357]
106 Patent	
Claim 8: t_{max} about 1.0 hours to about 5.5 (no dose)	

(A14824; A1816:14-1817:4; A13382-98; A14490-97; A14498-523.)

Claim 16 of the '106 patent is the sole asserted bioavailability claim and requires a bioavailability of tranexamic acid of greater than 40%. Such a limitation bears no novelty in view of the fact that the prior art disclosed bioavailability of almost 40%, considering recovery and half live. (A1817:6-14; A11490-534; A13629-37; A13382-98; A24835.)

The lack of novelty of these claims is also supported by the fact that the inventors of the patents-in-suit claimed the pharmacokinetic properties of the claimed invention are identical to the prior art. (A9196; A10734-35; A6948.) In fact, using available data and a well-known computer program, the inventors predicted these parameters before they gave even one tablet to a patient in a clinical trial. (A894:13-895:18.)

F. Ferring failed to overcome a strong showing of obviousness with any secondary considerations.

Where a claim is *prima facie* obvious, the patentee may attempt to rebut that conclusion by presenting secondary considerations of nonobviousness. *WMS*

Gaming Inc. v. Int'l Game Tech., 184 F.3d 1339, 1359 (Fed. Cir. 1999). When a patentee attempts to rely on unexpected results of a claimed invention, the patentee must "show that the claimed invention exhibits some *superior property or advantage* that a person of ordinary skill in the art would have found surprising or unexpected" compared to the prior art. *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (internal quotation marks omitted, emphasis added).

Ferring provided no evidence at trial supporting any arguments regarding commercial success, long-felt but unsolved need, skepticism and praise, copying, or failure of others. There is no evidence in this record of secondary considerations of obviousness that would overcome the strong showing of invalidity.

CONCLUSION

For the foregoing reasons, Watson very respectfully requests that this Court reverse the district court's judgment that Watson's accused products infringe any of the asserted claims. Watson also requests that this Court find that the asserted claims of the patents-in-suit are invalid as obvious. Finally, Watson requests that this Court reverse the injunction and resetting order injunction.

Dated: May 1, 2014

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ADDENDUM

UNITED STATES DISTRICT COURT

DISTRICT OF NEVADA

FERRING B.V., Plaintiff, vs. WATSON LABORATORIES, INC. - (FL) et al., Defendants.	3:11-cv-00481-RCJ-VPC **ORDER**
FERRING B.V., Plaintiff, vs. APOTEX, INC. et al., Defendants.	3:11-cv-00485-RCJ-VPC **ORDER**
FERRING B.V., Plaintiff, vs. WATSON PHARMACEUTICALS, INC. et al., Defendants.	3:11-cv-00853-RCJ-VPC **ORDER**
FERRING B.V., Plaintiff, vs. APOTEX, INC. et al., Defendants.	3:11-cv-00854-RCJ-VPC **ORDER**

These four consolidated cases arise out of Defendants' application with the Food and Drug Administration ("FDA") to manufacture and sell generic versions of a patented drug. Pending before the Court are a Motion to Stay (ECF No. 463), a Motion to Reconsider (ECF No. 465), two Motions to Strike (ECF Nos. 474, 477), and nine Motions to Seal (ECF Nos. 462, 464, 467, 471, 476, 478, 480, 482, 485).

I. FACTS AND PROCEDURAL HISTORY

These cases arise out of the alleged infringement of Plaintiff Ferring B.V.'s ("Ferring") U.S. Patent No. 7,947,739 for tranexamic acid tablets sold under the trademark Lysteda® (the "'739 Patent" or "Tablet Patent"), (*see* Compl. ¶¶ 13–17, July 7, 2011, ECF No. 1; Compl. ¶¶ 9–13, July 8, 2011, ECF No. 1 in Case No. 3:11-cv-00485), and the alleged infringement of Ferring's U.S. Patent No. 8,022,106 for tranexamic acid formulations and methods of treating menorrhagia therewith (the "'106 Patent" or "Formulas and Treatment Patent"), (*see* Compl. ¶¶ 13–17, Nov. 25, 2011, ECF No. 1 in Case No. 3:11-cv-00853; Compl. ¶¶ 9–13, Nov. 25, 2011, ECF No. 1 in Case No. 3:11-cv-00854).[1] In the '481 and '485 Cases, respectively, Ferring sued several Watson Labs entities (collectively, "Watson Defendants") and several Apotex entities (collectively, "Apotex Defendants") in this Court for infringing the '739 Patent. In the '853 and '854 Cases, respectively, Ferring sued several Watson Defendants and several Apotex Defendants in this Court for infringing the '106 Patent.

The Court consolidated the four cases, with the '481 Case as the lead case. It also granted motions to dismiss the counterclaims for invalidity and to strike affirmative defenses for invalidity in the '481 and '854 Cases, with leave to amend. The Court ruled that affirmative defenses must specify a distinct legal theory of invalidity under Rule 8(c) but need not be pled according to the *Iqbal* plausibility standard, as the counterclaims must be under Rule 8(a).

[1]Unless otherwise noted, the docket numbers in this document refer to Case No. 3:11-cv-00481.

Watson Defendants and Apotex Defendants amended their answers and counterclaims, accordingly. (*See* ECF Nos. 93, 94). Apotex Defendants later further amended its answer and counterclaim. The Court denied motions to dismiss the amended counterclaims for invalidity. The Court held a *Markman* hearing and issued a claim construction order. The Court held a bench trial and gave its findings of fact and conclusions of law from the bench, requesting counsel to draft a written order. The parties have since filed several motions.

II. DISCUSSION

Before addressing the other motions, the Court will grant the nine motions for leave to file those motions and related pleadings under seal.

A. Motion to Stay and Motion to Reconsider

Watson asks the Court to stay judgment pending appeal. The Court denies the motion. Watson argues that Ferring will not be irreparably harmed by a stay because: (1) under an agreement with a third party, Ferring would have saved $12.5 million upon the entry of a generic competitor into the market before May 13, 2013; and (2) the entry of a generic competitor into the market can actually benefit a brand name product, and that is, according to Watson, the case here. As to the first argument, it is not clear whether Ferring was able to take advantage of its alleged contractual provision with the third party. Even if it were so, that issue is settled. Ferring either did or did not avoid the additional $12.5 million payment to the third party based upon Watson's pre-May 13, 2013 marketing of its infringing product. The harm to Ferring going forward is from further competition by an infringing product. Also, even assuming for the sake of argument that all of Ferring's profit from Lysteda could be attributed to Watson's entry into the market, an infringement defendant cannot argue that the patentee has not been harmed by infringement simply because his sales have increased. The harm is not purely economic but also in the loss of good faith with the consuming public that comes from being an innovator with an exclusive product. That good faith carries forward to future endeavors of the company unrelated

to the sale of a particular product. Moreover, Watson's argument that as a competitor it actually benefitted Ferring implicitly admits that Watson's marketed product infringed Ferring's patent(s). That admission also severely damages Watson's argument that its ANDA filing did not infringe Ferring's patents under 35 U.S.C. § 271(e)(2). *See Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1567–68 (Fed. Cir. 1997) ("The relevant inquiry is whether the patentee has proven by a preponderance of the evidence that the alleged infringer will likely market an infringing product."). Watson has not shown that it is likely to succeed on the merits of the appeal.

B. Motion to Reconsider

This issue is unripe. Because the Court has not yet entered any injunction but only indicated its tentative inclinations, the Court will not "reconsider" entry of a potential future injunction.

C. Motions to Strike

First, Watson asks the Court to strike a letter to the Court from Ferring concerning the substantive issue of a request for a preliminary injunction as an improper communication with the Court. The Court denies the motion. As Ferring notes, the letter accompanied the proposed form of judgment the Court requested Ferring to file and did not constitute a request for any separate injunction.

Second, Apotex asks the Court to strike Ferring's proposed findings of fact and conclusions of law as to Apotex, because the Court indicated that it intended to rule in favor of Apotex given Apotex's post-trial agreement to amend its ANDA to exclude the possibility that FDA approval would permit Apotex to sell products within the scope of Ferrings claims. Apotex argues that the Court instructed Ferring and Apotex to agree upon an appropriate stipulation but that Ferring instead simply wrote the proposed judgment as if there were to be no stipulation but Apotex simply lost at trial. The Court addressed the issue at the March 5, 2013 hearing.

CONCLUSION

IT IS HEREBY ORDERED that the Motions to Seal (ECF Nos. 462, 464, 467, 471, 476, 478, 480, 482, 485) are GRANTED.

IT IS FURTHER ORDERED that the Motion to Stay (ECF No. 463), the Motion to Reconsider (ECF No. 465), and the Motions to Strike (ECF Nos. 474, 477) are DENIED.

IT IS SO ORDERED.

Dated this 24th day of March, 2014.

ROBERT C. JONES
United States District Judge

UNITED STATES DISTRICT COURT

DISTRICT OF NEVADA

FERRING B.V., Plaintiff, v. WATSON LABORATORIES, INC. - FLORIDA, APOTEX INC. and APOTEX CORP., Defendants.	Consolidated Case Nos: 3:11-cv-00481-RCJ-VPC 3:11-cv-00485-RCJ-VPC 3:11-cv-00853-RCJ-VPC 3:11-cv-00854-RCJ-VPC 3:12-cv-01935-RCJ-VPC 3:12-cv-01941-RCJ-VPC **ORDER AND FINAL JUDGMENT AS TO WATSON LABORATORIES, INC. - FLORIDA**

1. For the reasons set forth in the Findings of Fact and Conclusions of Law to be issued separately by the Court, the Court holds that Watson's ANDA No. 202093 infringes the asserted claims of the '739, '106 and '795 patents under 35 U.S.C. § 271(e)(2). The Court additionally holds that Watson's generic tranexamic acid tablets infringe the asserted claims of the '739, '106 and '795 patent under 35 U.S.C. § 271(a).

2. Under 35 U.S.C. § 271(e)(2), it is an act of infringement to submit, *inter alia*, an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act if the purpose of such submission is to obtain approval to engage in the commercial manufacture, use, or sale of a drug claimed in a patent or the use of which is claimed in a patent before the expiration of such patent. Under section 271(e)(4)(A), the statute states that "[f]or an act of infringement under paragraph (2) . . . the court **shall** order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of

the expiration of the patent which has been infringed." (Emphasis added.) Indeed, the Federal Circuit has stated that section 271(e)(4)(A) requires a district court to order the effective date of approval to be a date that is not earlier than the date the infringed patent expires. *See, e.g., In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1367 (Fed. Cir. 2008); *see also Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 2007 U.S. Dist. LEXIS 19494, at *3-6 (D.N.J. 2007). A permanent injunction is appropriate under section 271(e)(4)(B) for infringement under section 271(e)(2) and under section 283 for infringement under 35 U.S.C. § 271(a). *See, e.g., Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 2010 WL 4596324, at *36 (D.N.J. 2010).

3. Accordingly, the Court enters the following limited injunction as to Watson. The Court holds that the Federal Food and Drug Administration ("FDA") must reset the approval date of Watson's generic tranexamic acid tablet ANDA to a date no earlier than the expiration of the patents-in-suit – i.e., March 4, 2025. The Court likewise enjoins Watson and its officers, agents, attorneys, and employees and those acting in privity or concert from seeking, obtaining or maintaining approval of Watson's infringing generic tranexamic acid tablet ANDA during the remaining term of the patents-in-suit. Finally, the Court enjoins Watson and its officers, agents, attorneys, and employees and those acting in privity or concert with it from making, using, offering to sell, or selling, within the United States or importing into the United States Watson's uncoated and coated generic tranexamic acid tablets during the remaining term of the patents-in-suit. The Court notes that this injunction does not preclude Watson from seeking FDA approval of an ANDA containing an amended ANDA specification, by submitting a major amendment or a new ANDA, that excludes the possibility of infringing products. If Watson seeks such FDA approval, it shall copy counsel for Ferring on this correspondence with the FDA and include in its submission to the FDA a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a "Paragraph

IV Certification") explaining its basis for its contention that its ANDA specification excludes the possibility of infringing products.

IT IS SO ORDERED.

Dated this 14th day of April, 2014.

ROBERT C. JONES
United States District Judge


US007947739B2

(12) **United States Patent**
Moore et al.

(10) **Patent No.: US 7,947,739 B2**
(45) **Date of Patent: May 24, 2011**

(54) **TRANEXAMIC ACID FORMULATIONS**

(75) Inventors: **Keith A. Moore**, Loveland, OH (US); **Ralph A. Heasley**, Webster Grove, MO (US); **Jeffrey S. Greiwe**, Ft. Thomas, KY (US); **John W. Facemire**, Douglasville, GA (US); **Jason D. Modest**, Minneapolis, MN (US)

(73) Assignee: **Ferring B.V.**, Hoofddorp (NL)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **12/714,181**

(22) Filed: **Feb. 26, 2010**

(65) **Prior Publication Data**

US 2010/0143468 A1 Jun. 10, 2010

Related U.S. Application Data

(63) Continuation of application No. 12/433,510, filed on Apr. 30, 2009, which is a continuation-in-part of application No. 12/228,489, filed on Aug. 13, 2008, which is a continuation of application No. 11/072,194, filed on Mar. 4, 2005, now abandoned.

(60) Provisional application No. 60/550,113, filed on Mar. 4, 2004, provisional application No. 60/592,885, filed on Jul. 30, 2004.

(51) **Int. Cl.**
A61K 31/19 (2006.01)
A61K 31/195 (2006.01)

(52) **U.S. Cl.** **514/574**; 514/561

(58) **Field of Classification Search** 514/561, 514/574

See application file for complete search history.

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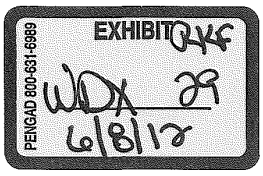
(57) **ABSTRACT**

Disclosed are modified release oral tranexamic acid formulations and methods of treatment therewith.

19 Claims, 7 Drawing Sheets



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Defendant Watson
Trial Exhibit

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Investigative report dated Apr. 7, 2010 and prepared by Chief Investigator D.C. Sharma of ClueWise Services, Pvt. LTD. (India) concerning information sought on Mefro Pharmaceuticals and Terrance Pharma (both of India), specifically in relation to a Trexamic Rx product (tranexamic acid) (Reference All).

* cited by examiner

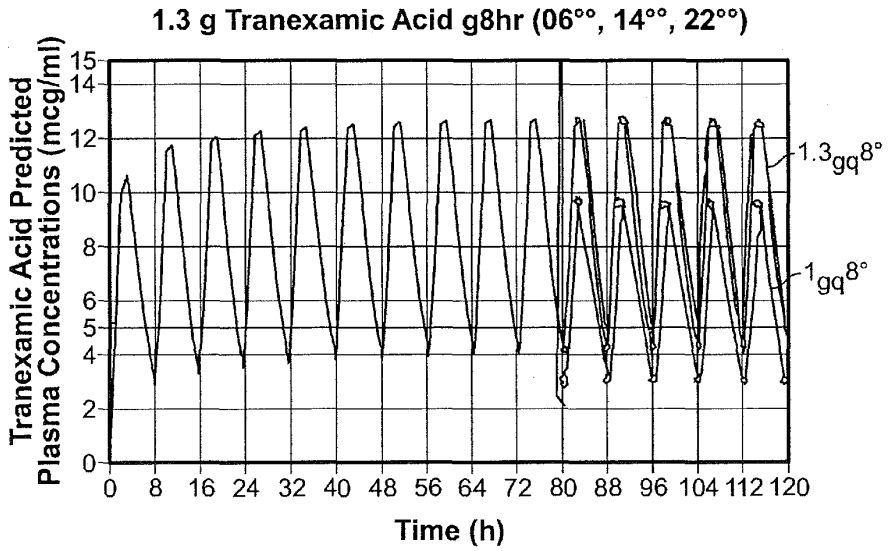
1.3 g Tranexamic Acid g8hr (06°°, 14°°, 22°°)
Tranexamic Acid Predicted Plasma Concentrations (mcg/ml)
0 2 4 5 6 8 10 12 14 15
0 8 16 24 32 40 48 56 64 72 80 88 96 104 112 120
Time (h)
1.3gq8°
1gq8°

FIG. 1

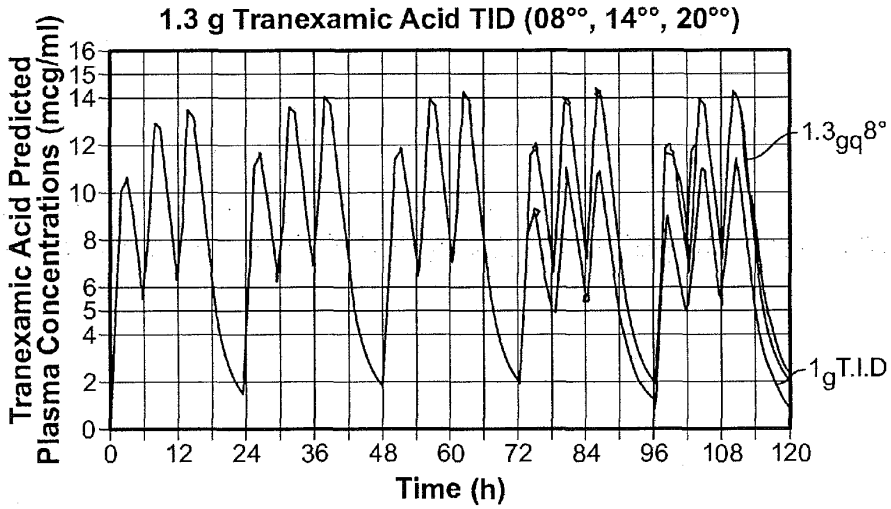
1.3 g Tranexamic Acid TID (08°°, 14°°, 20°°)
Tranexamic Acid Predicted Plasma Concentrations (mcg/ml)
0 2 4 5 6 8 10 12 14 15 16
0 12 24 36 48 60 72 84 96 108 120
Time (h)
1.3gq8°
1gT.I.D

FIG. 2

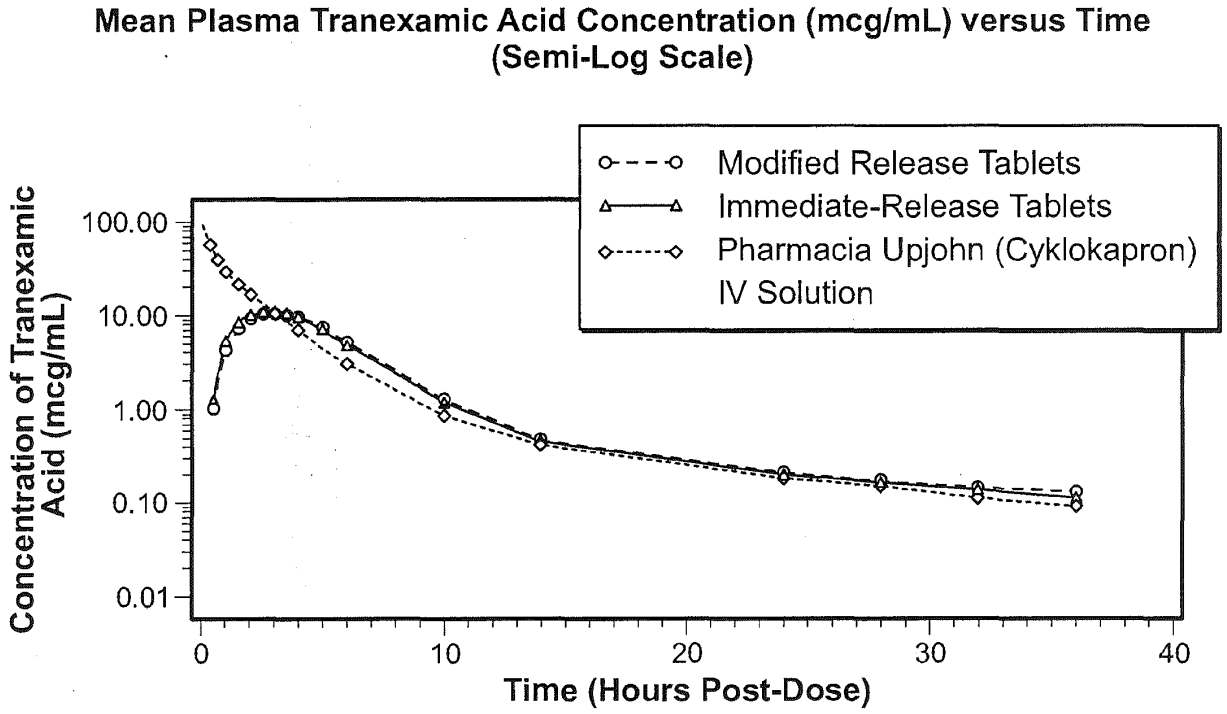

FIG. 3

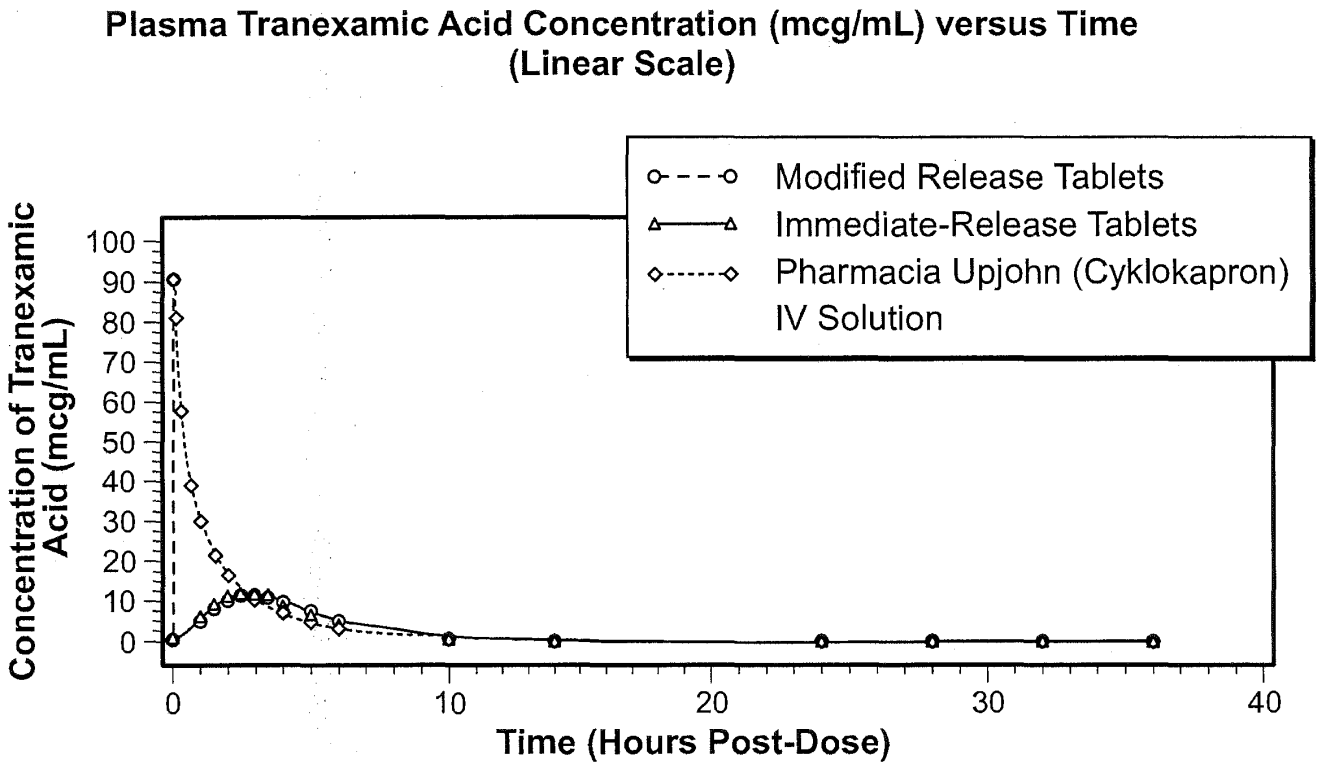

FIG. 4

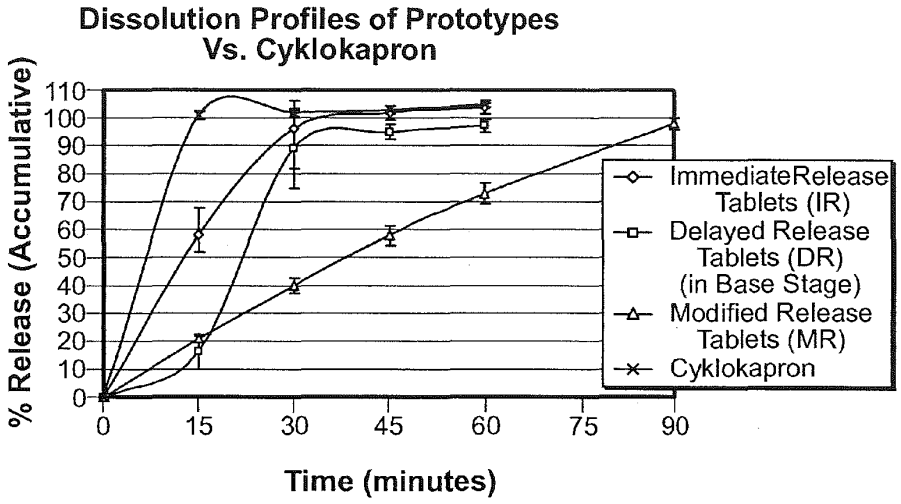
Dissolution Profiles of Prototypes
Vs. Cyklokapron
% Release (Accumulative)
110
100
90
80
70
60
50
40
30
20
10
0
0
15
30
45
60
75
90
Time (minutes)
ImmediateRelease Tablets (IR)
Delayed Release Tablets (DR) (in Base Stage)
Modified Release Tablets (MR)
Cyklokapron

FIG. 5

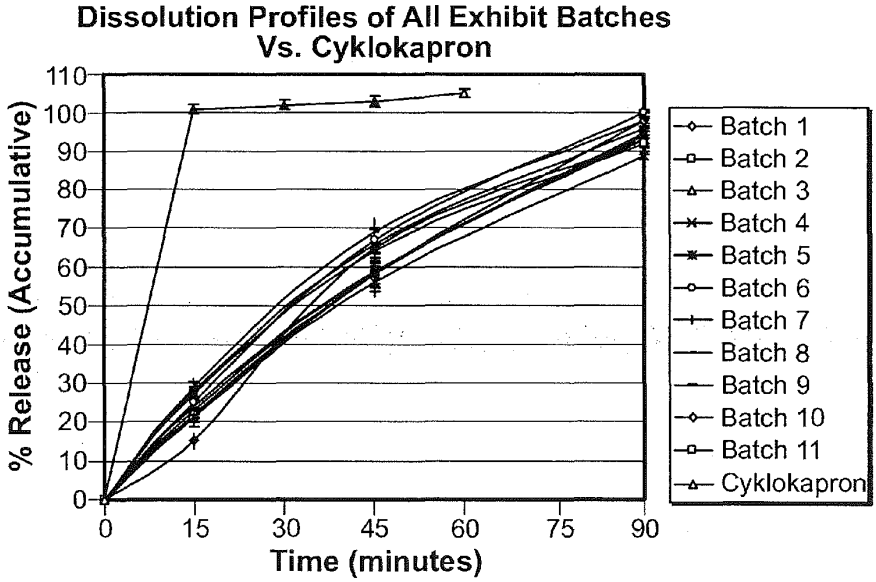
Dissolution Profiles of All Exhibit Batches
Vs. Cyklokapron
% Release (Accumulative)
110
100
90
80
70
60
50
40
30
20
10
0
0
15
30
45
60
75
90
Time (minutes)
Batch 1
Batch 2
Batch 3
Batch 4
Batch 5
Batch 6
Batch 7
Batch 8
Batch 9
Batch 10
Batch 11
Cyklokapron

FIG. 6

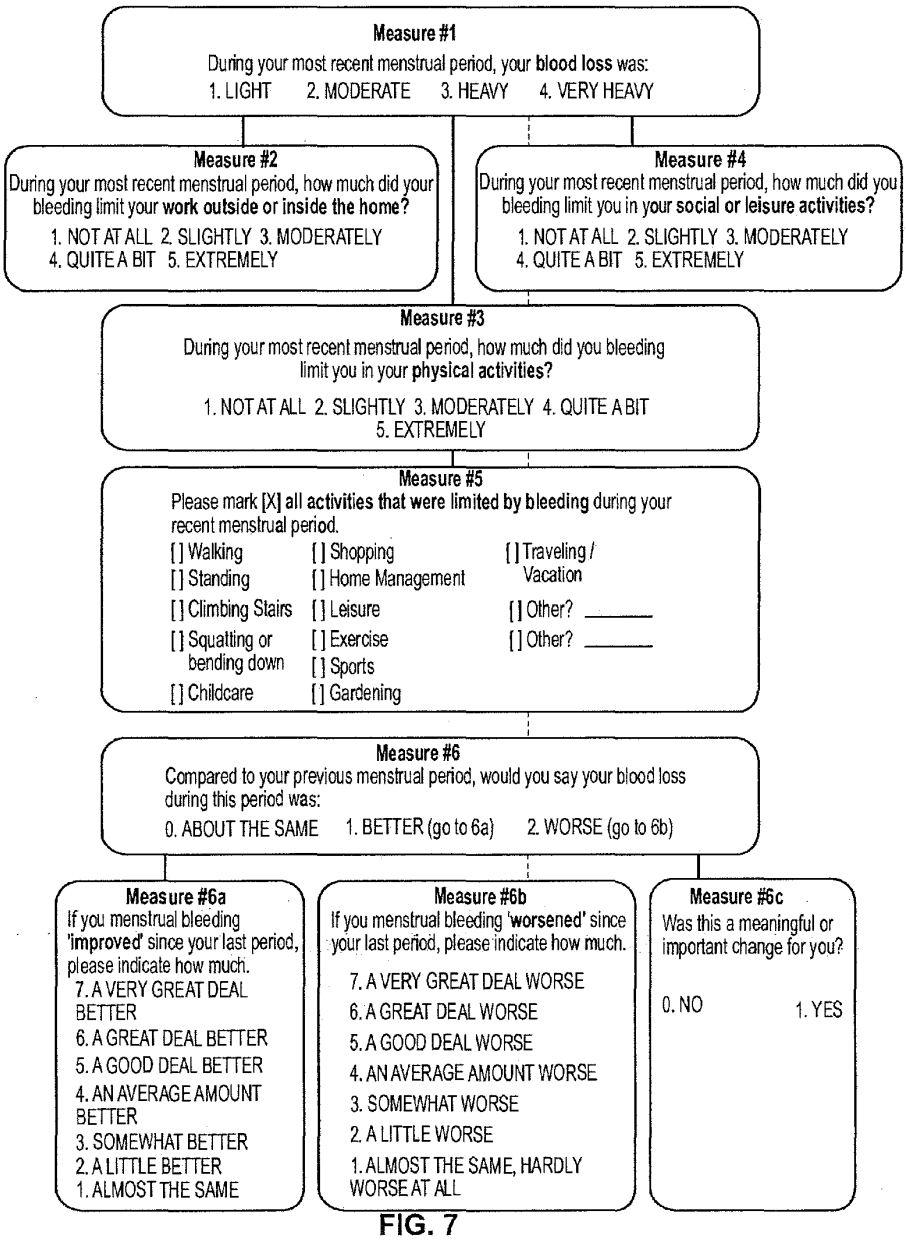
Measure #1
During your most recent menstrual period, your blood loss was:
1. LIGHT 2. MODERATE 3. HEAVY 4. VERY HEAVY
Measure #2
During your most recent menstrual period, how much did your bleeding limit your work outside or inside the home?
1. NOT AT ALL 2. SLIGHTLY 3. MODERATELY
4. QUITE A BIT 5. EXTREMELY
Measure #4
During your most recent menstrual period, how much did you bleeding limit you in your social or leisure activities?
1. NOT AT ALL 2. SLIGHTLY 3. MODERATELY
4. QUITE A BIT 5. EXTREMELY
Measure #3
During your most recent menstrual period, how much did you bleeding limit you in your physical activities?
1. NOT AT ALL 2. SLIGHTLY 3. MODERATELY 4. QUITE A BIT
5. EXTREMELY
Measure #5
Please mark [X] all activities that were limited by bleeding during your recent menstrual period.
[ ] Walking
[ ] Standing
[ ] Climbing Stairs
[ ] Squatting or bending down
[ ] Childcare
[ ] Shopping
[ ] Home Management
[ ] Leisure
[ ] Exercise
[ ] Sports
[ ] Gardening
[ ] Traveling / Vacation
[ ] Other? _____
[ ] Other? _____
Measure #6
Compared to your previous menstrual period, would you say your blood loss during this period was:
0. ABOUT THE SAME 1. BETTER (go to 6a) 2. WORSE (go to 6b)
Measure #6a
If you menstrual bleeding 'improved' since your last period, please indicate how much.
7. A VERY GREAT DEAL BETTER
6. A GREAT DEAL BETTER
5. A GOOD DEAL BETTER
4. AN AVERAGE AMOUNT BETTER
3. SOMEWHAT BETTER
2. A LITTLE BETTER
1. ALMOST THE SAME
Measure #6b
If you menstrual bleeding 'worsened' since your last period, please indicate how much.
7. A VERY GREAT DEAL WORSE
6. A GREAT DEAL WORSE
5. A GOOD DEAL WORSE
4. AN AVERAGE AMOUNT WORSE
3. SOMEWHAT WORSE
2. A LITTLE WORSE
1. ALMOST THE SAME, HARDLY WORSE AT ALL
Measure #6c
Was this a meaningful or important change for you?
0. NO 1. YES

FIG. 7

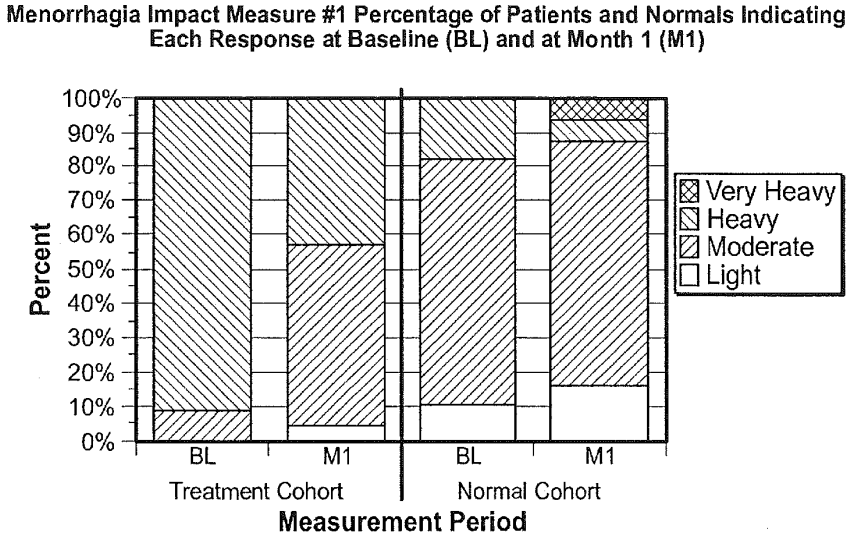
Menorrhagia Impact Measure #1 Percentage of Patients and Normals Indicating Each Response at Baseline (BL) and at Month 1 (M1)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percent
BL
M1
BL
M1
Treatment Cohort
Normal Cohort
Measurement Period
Very Heavy
Heavy
Moderate
Light

FIG. 8

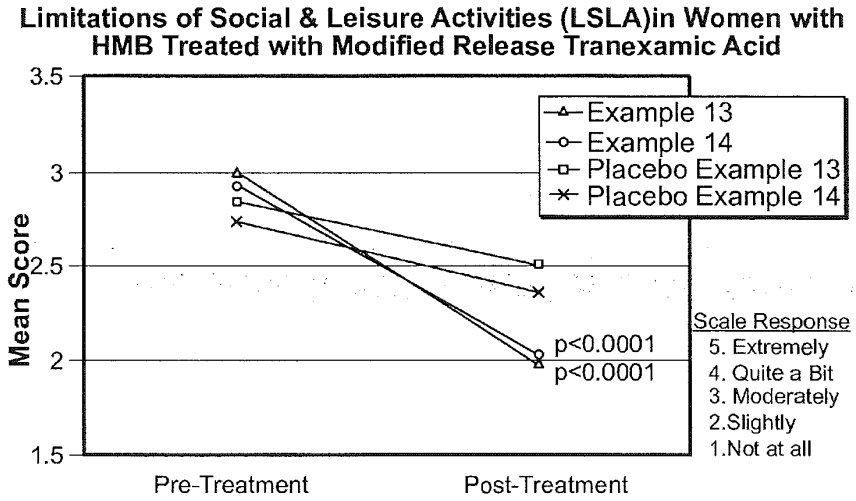
Limitations of Social & Leisure Activities (LSLA)in Women with HMB Treated with Modified Release Tranexamic Acid
3.5
3
2.5
2
1.5
Mean Score
Example 13
Example 14
Placebo Example 13
Placebo Example 14
p<0.0001
p<0.0001
Scale Response
5. Extremely
4. Quite a Bit
3. Moderately
2.Slightly
1.Not at all
Pre-Treatment
Post-Treatment

FIG. 9

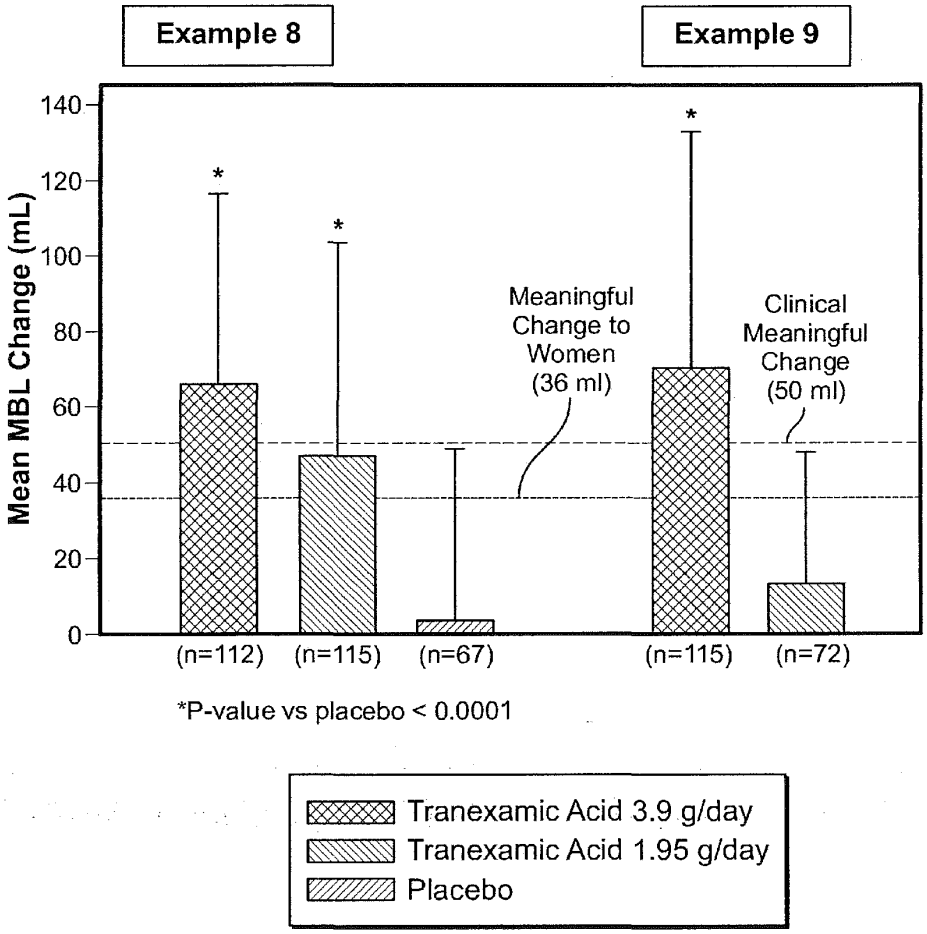
Example 8
Example 9
Mean MBL Change (mL)
140
120
100
80
60
40
20
0
*
*
*
Meaningful Change to Women (36 ml)
Clinical Meaningful Change (50 ml)
(n=112)
(n=115)
(n=67)
(n=115)
(n=72)
*P-value vs placebo < 0.0001
Tranexamic Acid 3.9 g/day
Tranexamic Acid 1.95 g/day
Placebo

FIG. 10

TRANEXAMIC ACID FORMULATIONS

This application is a continuation of U.S. patent application Ser. No. 12/433,510, filed Apr. 30, 2009, which is a continuation-in-part of U.S. patent application Ser. No. 12/228,489, which is a continuation of U.S. patent application Ser. No. 11/072,194 filed Mar. 4, 2005, now abandoned, which claims the benefit of U.S. Provisional Application No. 60/550,113, filed Mar. 4, 2004, and U.S. Provisional Application No. 60/592,885, filed Jul. 30, 2004, the disclosures of which are both hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

The invention is directed to modified release oral tranexamic acid formulations that preferably minimize or eliminate undesirable side effects and methods of treatment with these formulations.

BACKGROUND OF THE INVENTION

Tranexamic acid (trans-4-(aminomethyl)cyclohexanecarboxylic acid, Cyklokapron® (Pfizer) is an antifibrinolytic agent. That is, it helps to prevent lysis or dissolution of a fibrin clot which forms in the normal physiologic process of hemostasis. Its mechanism of action is as a competitive inhibitor of plasminogen activation, and as a noncompetitive inhibitor of plasmin; both plasminogen and plasmin are activators of fibrinolysis and active clot-lysing agents. Tranexamic acid thus helps to stabilize fibrin clots, which in turn maintains coagulation and helps to control bleeding.

Tranexamic acid is used to control excess bleeding, for example, excess bleeding that occurs during dental procedures in hemophiliacs and for heavy bleeding during menstruation (menorrhagia). Women suffering from menorrhagia are typically treated orally with 500 mg tranexamic acid tablets administered three or four times daily with a total daily dose ranging from 3 grams/day (two tablets every eight hours) to 6 grams/day (three tablets every six hours). However, this treatment may cause adverse gastrointestinal reactions, including nausea, vomiting, diarrhea, and cramping, etc. These gastrointestinal side effects are due to the quantity of tranexamic acid and/or rapid rate of release of tranexamic acid into the stomach with each dose, as well as the large quantity of excipients used in the tablet formulation that are introduced into the stomach. Such side effects, in addition to the cramping, bloating, pain, and other symptoms that may accompany menses, are undesirable, and a formulation of tranexamic acid is needed which will reduce or eliminate these side effects.

Menstrual Bleeding

Menstrual Bleeding disorders encompass a number of conditions including bleeding associated with uterine fibroids, endometriosis, or bleeding as a result of deficiencies in the clotting process for example, von-Willebrand's disease. Studies suggest that as many as 11% of the women who experience heavy menstrual bleeding, suffer from an inherited bleeding disorder such as von Willebrand's disease. Excessive Menstrual Bleeding is menstruation at relatively regular intervals but with excessive blood loss over the menses period which may be prolonged. Heavy Menstrual Bleeding (also referred to as "Menorrhagia") is a serious, persistent, and recurrent medical condition that is one of the most common complaints encountered by gynecologists and primary care physicians (Palep-Singh, 2007). A 2005 survey of 273 obstetrician/gynecologists found that they see an average of 18 to 25 symptomatic patients per month. Heavy Menstrual Bleeding is a hyperfibrinolytic condition defined as cyclic, normal intervals of menstruation with excessive volume. Menorrhagia is often associated with a disruption in daily routines, work, and sexual activity leading to a significant decrease in health-related quality of life and time lost from work or school. While Menorrhagia is rarely life threatening, when undiagnosed and untreated, it may over time cause iron deficiency anemia and increased fatigue, both of which affect normal life activities, relationships, social activities, and various aspects of mental well-being (irritation, anxiety). Left untreated it may be associated with subsequent morbidity including dysmenorrhea, hospitalization, red blood cell transfusions and chronic pain. Annually, approximately 10% of women of reproductive age report Menorrhagia (Rees 1991; van Eijkeren, 1992) and according to the Center for Disease Control (CDC), 3 million women of reproductive age report Menorrhagia yearly, 60% of which have no known etiology. Studies report that as many as thirty percent of premenopausal women perceive their menses to be excessive.

Women suffering from menorrhagia often have greater uterine fibrinolytic activity than women with normal cyclic menstrual blood loss (MBL). High concentrations of plasminogen activators are found in both the uterus and menstrual fluid (Albrechtsen, 1956a,b). Rybo (1966) found significantly higher concentration of endometrial plasminogen activators in women with excessive menstrual bleeding compared to women with normal menstrual loss.

Causes of Menorrhagia include pelvic diseases (myomata [fibroids], adenomyosis or uterine polyps), intrauterine contraceptive devices, and systemic disorders (coagulopathies such as thrombocytopenia or von Willebrand's disease, and hypothyroidism). In contrast to menorrhagia, the term 'dysfunctional uterine bleeding' refers to excessive, prolonged or irregular bleeding from the endometrium that is unrelated to systemic disease (Wathen, 1995), and is usually associated with anovulation. Menorrhagia is also distinguished from other ovulatory bleeding disorders, such as metrorrhagia (intermenstrual bleeding), menometrorrhagia (irregular heavy menstrual bleeding) and polymenorrhea (menstrual cycle less than 21 days).

Diagnosis of Menstrual Blood Loss

In clinical trials, menstrual blood loss (MBL) is usually determined by measuring the amount of hemoglobin recovered from sanitary products during the menstrual cycle, using the alkaline hematin method (Fraser, 1994). However, it is important to remember that blood accounts for only about 50% of total menstrual flow, with endometrial transudate accounting for the remainder (Fraser, 1994). Total menstrual flow can be estimated by weighing of sanitary products or by comparisons with a pictorial blood loss assessment chart. However, the use of these quantitative and semi-quantitative methods is not practical in non-trial settings. Rather, the diagnosis of Menorrhagia in the healthcare clinic is made by medical providers on the basis of patient's perceived and self-reported medical history, routine laboratory assessments of the patient's general health status, and gynecological examinations.

Clinically heavy menstrual bleeding is sometimes defined as total blood loss exceeding about 80 ml per cycle or menses lasting longer than seven days. The volume lost however, varies widely. Clinically losses from about 30 ml to 60 ml, 60 to 80 ml, 80 to 100 ml, to as high as 1000 ml per cycle are observed. Menstrual blood losses of 50 to 60 ml are associated with a negative iron balance and iron deficiency anemia is diagnosed in about 67% of the women who lose an excess

of 80 ml per day. Other criteria for diagnosing the condition include measuring the number and size of blood clots in the meneges, or monitoring the use of pads or tampons. It is estimated that perhaps only ten percent of women who perceive their loss to be excessive actually fall within the clinical definition. The 80 ml definition has been repeatedly questioned, and alternative definitions broadened the blood loss range used for patient evaluations.

Blood loss volume assessments commonly require the collection and preservation of menstrual pads or tampons, the extraction of the pads and the accurate measurement of the blood content. Women are instructed to collect all sanitary towels and tampons during the course of the menstrual diagnosis period or the course of a clinical study period. Blood loss can be measured by extraction of the blood from the sanitary material with 5% sodium hydroxide followed with a spectrophotometric measurement of hematin at a wavelength of about 540 nm. The total blood loss can be calculated for an individual by comparison of the patients plasma blood hemoglobin measurement with the collected hemoglobin values.

The collection of the blood sample discourages the routine use of the test in the diagnosis or in the treatment of the condition. In the course of a routine visit with a physician other blood work may be appropriate but lacks a casual relation to the heavy bleeding disorder. The battery of routine laboratory tests may include patient blood hemoglobin, haematocrit, platelet count, bilirubin, serum creatinine and serum ferritin. In sum, diagnosis in the routine course of practice relies heavily on the woman's perception of the volume of blood lost during menses.

Diagnosis and Treatment of Heavy Menstrual Bleeding Disorders (Menorrhagia)

A number of medical and surgical interventions are available to treat menstrual bleeding disorders. Currently available non-surgical treatments for heavy bleeding disorders, include, hormonal treatments (e.g., oral contraceptives), high-dose progestin therapy, desmopressin acetate, ethamsylate, nonsteroidal anti-inflammatory drugs (NSAIDs), the antifibrinolytic drugs aminocaproic acid and tranexamic acid. Even with the drug treatments available, surgery remains a common treatment.

Although not approved for menorrhagia in the US, use of oral contraceptives for menorrhagia is widely accepted. Oral contraceptives may not be a preferred therapy for some women because of age (younger females), unwanted side effects (nausea and vomiting, breakthrough bleeding, weight change, migraines and depression), and safety concerns (increased risk of thromboembolism, stroke, myocardial infarction, hepatic neoplasia and gall bladder disease). High-dose progestin (synthetic versions of the hormone progesterone) may also be given to women with menorrhagia, either orally or by a progestin-releasing device inserted into the uterus (intrauterine device). Side effects include nausea, bloating, mood changes, and breast tenderness.

Although it is typically a last resort, desmopressin acetate is sometimes used to help lighten menstrual flow in women with menorrhagia. The effectiveness of desmopressin is thought to vary between individuals. Side effects include headache, tachycardia, facial flushing, and rare reports of thromboembolism.

NSAIDs are sometimes used to treat menorrhagia as they may reduce blood flow while providing analgesia for pain associated with the condition (Shaw, 1994). Side effects associated with chronic NSAID use include gastrointestinal bleeding, ulceration, and perforation; and renal effects such as hyperkalemia, hyponatremia, acute renal insufficiency, interstitial nephritis, and renal papillary necrosis.

Hysterectomy or endometrial resection are options if other forms of therapy are not effective or are unsuitable for some reason. Possible surgical complications include infection, uterine perforation, and other complications associated with major surgery.

Antifibrinolytic drugs, such as ε-aminocaproic acid and tranexamic acid (immediate-release formulation) have been used to treat HMB in women with or without a diagnosed bleeding disorder (van Eijkeren, 1992; Bonnar, 1996; Vermylen, 1968; Nilsson, 1965). The available evidence from published literature suggests that tranexamic acid at doses of ~4 g/day (typically 1 g every 6 hours) is effective in the treatment of HMB and is associated with few side effects (Callender, 1970; Dunn, 1999; Edlund, 1995; Preston, 1995). In Sweden, the average dose of tranexamic acid to treat HMB is 3.9 g/day (Rybo, 1991). Thus, tranexamic acid is used extensively in Europe, Canada, Asia, Japan, Australia and New Zealand to treat menorrhagia, but is not approved for this indication in the US.

Tranexamic acid is a competitive inhibitor of plasminogen activation (see review by Dunn, 1999). Binding of tranexamic acid to plasminogen does not prevent conversion of plasminogen to plasmin by tissue plasminogen activator, but the resulting plasmin/tranexamic acid complex is unable to bind to fibrin. Thus, enzymatic breakdown of fibrin by plasmin (fibrinolysis) is inhibited. At higher concentrations, tranexamic acid is also a noncompetitive inhibitor of plasmin.

Before medical and surgical interventions can be initiated, diagnosis of a heavy menstrual bleeding disorder must be accomplished.

Diagnosis and treatment of disease often depends on the patient's perception and subsequent description of symptoms, the physician's evaluation of the patient's description, the physician observations of the patient and laboratory test results. Menstrual bleeding disorders do not lend themselves to physician observation or to routine laboratory testing. Patient observations and the physician's evaluation of the patient's description are subjective and thus variable. In addition a women's medical history has been found to be a poor predictor of menstrual blood loss. Neither the duration of menses nor the number of sanitary pads worn accurately corresponds to the woman's actual menstrual blood loss (Chimbira, Haynes, year). An objective assessment of blood loss using the alkaline haematin assay has been shown to be reproducible but it is not suited for routine clinical use by healthcare providers. To date no effective instrument for reliably diagnosing and/or monitoring the treatment of menstrual bleeding disorders has been developed despite the significant number of women who suffer from these conditions.

Previously, studies have focused on the impact of symptoms of bleeding disorders on patients' health related quality of life. As the effects of menstrual bleeding disorders are primarily symptomatic, the subjective outcome namely symptom alleviation, cannot be objectively measured. In research from European countries where the antifibrinolytic drug tranexamic acid is currently available, treatment with this antifibrinolytic has reduced heavy menstrual bleeding by 40-50% and improved the health-related quality of life of affected women on measures of social activity, work performance, productivity, cleanliness, overall functioning and tiredness.

Jenkinson et al, Quality in Health Care 1996; 5; 9-12 evaluated the validity and internal reliability of the short form-36 (SF36) health survey questionnaire in women presenting with menorrhagia. The study concluded that several questions on the questionnaire were difficult to answer for patients with heavy menstrual bleeding. Such problems were suggested as

possible interferences with the validity of the measure. Jenkinson warns that because a subjective measure works well in one population or with one group, this cannot be taken to imply its appropriateness for all groups or conditions.

Edlund, in an abstract from a seminar on Dysfunctional Uterine Bleeding, Feb. 23, 1994, indicates that a questionnaire was used in a Swedish study of 2205 women who described their menstruation as excessive.

Winkler in a study based in part on the Edlund work, concluded that the treatment of heavy menstrual bleeding with tranexamic acid increased the quality of life of the treated patients. The Winkler study was an open label uncontrolled usage study which included 849 patients. A questionnaire was used prior to treatment and after the first and third menstruation. The study indicates that 80% of the women were satisfied with the treatment. The questionnaire used a series of eight question combined with an assessment by the patients of the change in quantity of menstrual flow.

Ruta, D. A., Quality of Life Research, 4, (33-40), 1995 finds that menorrhagia is a common problem in gynecological practice and that women seek professional help primarily because of the deleterious effect on their quality of life. Ruta recognizing the importance of evaluating the effectiveness of the treatments developed a questionnaire based on the type of questions frequently asked when taking a gynecological history. A series of questions were devised which assessed fifteen factors including the duration of the period, the regularity of the period, pain, problems with soiling/staining, interference with work, interference with leisure. Ruta concluded that the clinical questionnaire may be useful in selecting patients for hysterectomy and assessing the outcome of conservative treatment especially in combination with the SF-36 questionnaire.

Diagnostic Test for Menstrual Bleeding

The alkaline haematine test described above provides quantitative assessments of the extent of menstrual bleeding. This test allows the physician to diagnose and monitor the progress of a women's menstrual process. However the test is impractical and difficult to perform. The test requires women to capture used menstrual pads over the course of her period, preserve the samples in a condition such that the blood content within the pad may be accurately extracted and quantitated. Requesting a patient to perform menses sample collection may be practical in the course of a clinical trial where procedures are specified and monitored however, in routine medical practice, the use of such a test procedure to diagnose and monitor a women's menstrual bleeding is impractical and the data generated is unreliable.

The need remains to develop an assessment system which replaces previously studied diagnostic techniques and the alkaline haematine test and provides a reliable measure of both the occurrence of the disorder and the progress of the disorder. The present invention fills this need by providing a Heavy Menstrual Bleeding Instrument (HMBI) which is capable of diagnosing, and monitoring the treatment of a patient with a menstrual bleeding disorder.

There also remains a need to provide Heavy Menstrual Bleeding (HMB) therapy that is safe, efficacious and only administered during the monthly period of heavy menstruation, addresses the excessive fibrinolysis implicated in many causes of menorrhagia, and fills a currently recognized unmet medical need in the US. Therapy for HMB is expected to reduce the incidence and extent of iron-deficiency anemia, and to provide a nonhormonal medical therapy option in lieu of the numerous invasive procedures (e.g., transcervical endometrial resection) and major surgery (hysterectomy) performed annually.

SUMMARY OF THE INVENTION

Formulations of tranexamic acid which minimize or eliminate the undesirable gastrointestinal side effects in patients on oral tranexamic acid therapy, e.g. women treated for menorrhagia (heavy menstrual bleeding) are disclosed. The present invention is directed in part to a modified release formulation, formulated so that the release of tranexamic acid thereof from the dosage form occurs in a designed fashion to prevent a bolus of tranexamic acid being introduced into the stomach and available for dissolution in the gastric contents. Such modified release formulations reduce the concentration of tranexamic acid dissolved in the stomach contents such as e.g., preventing a large bolus of tranexamic acid being introduced in the stomach. The beneficial effect of this reduced tranexamic acid concentration is to lower the amount of tranexamic acid in the gastric contents so that there are fewer adverse effects with tranexamic acid therapy. This reduction in adverse effects preferably results in improved patient compliance with therapy, because preferably patients will not intentionally miss taking a dose to avoid these adverse side effects. Physicians will also preferably be more likely to initiate and maintain tranexamic acid treatment for their patients because of the reduced patient complaints.

It is an object of the invention to provide an oral dosage form comprising tranexamic acid which is suitable for administration on a two or three times a day basis to humans.

It is a further object of the invention to provide a modified release oral dosage form comprising tranexamic acid and a modified release material which provides for the modified release of the tranexamic acid and is suitable for administration on a two or three times a day basis.

It is a further object of certain embodiments of the present invention to provide a modified release oral dosage form comprising tranexamic acid and a modified release material which minimizes or eliminates the undesirable gastrointestinal side effects in patients on oral tranexamic acid therapy while maintaining or improving the therapeutic effect of tranexamic acid.

It is a further object of certain embodiments of the present invention to provide a method of treating a patient suffering from heavy menstrual bleeding (menorrhagia) by orally administering to the patient one or more dosage forms comprising tranexamic acid and a modified release material which provide(s) for therapeutically effective levels of tranexamic acid suitable for two or three times a day administration.

The above advantages and objects and others can be achieved by virtue of the present invention which is directed in part to a modified release oral dosage form comprising tranexamic acid or a pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis; said dosage form providing an in-vitro dissolution release rate of the tranexamic acid or pharmaceutically acceptable salt thereof, when measured by a USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C., of less than about 70% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes and about 100% by weight of said tranexamic acid or pharmaceutically acceptable salt thereof released by about 120 minutes.

In certain embodiments, the present invention is directed to a method of treating a patient in need of tranexamic acid or pharmaceutically acceptable salt thereof therapy comprising

administering to the patient about 1300 mg of tranexamic acid or pharmaceutically acceptable salt thereof in at least one oral dosage form comprising said tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides a mean maximum plasma concentration (C_{max}) of tranexamic acid of from about 5 to about 17.5 mcg/ml, preferably from about 6.5 to about 15 mcg/ml, more preferably from about 9 to about 14.5 mcg/ml after single dose oral administration to humans.

In certain embodiments, the invention is further directed to a method of treating a patient in need of tranexamic acid or pharmaceutically acceptable salt thereof therapy comprising administering to the patient about 1300 mg of tranexamic acid or pharmaceutically acceptable salt thereof in at least one oral dosage form comprising said tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides a mean maximum plasma concentration (C_{max}) of tranexamic acid of from about 5 to about 25 mcg/ml, preferably from about 10 to about 20 mcg/ml, more preferably from about 12.5 to about 17.5 mcg/ml, most preferably about 15 to about 17 mcg/ml after steady state oral administration to humans.

In certain embodiments, the modified release oral dosage form of the present invention provides a mean T_{max} of tranexamic acid at from about 1 to about 5.5 hours, preferably at from about 2 to about 4 hours, more preferably at from about 2 to about 3.5 hours after oral administration of the dosage form to humans.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides a dissolution release rate in-vitro of the tranexamic acid or pharmaceutically acceptable salt thereof when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. of less than about 40% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, less than about 70% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, and not less than 50% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides a dissolution release rate in-vitro of the tranexamic acid or pharmaceutically acceptable salt thereof when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. of about 0% to about 40% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, from about 20% to about 60% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 30 minutes, from about 40% to about 65% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, from about 50% to about 90% by weight tranexamic acid or pharmaceutically acceptable salt thereof release at about 60 minutes, and not less than 60% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, which provides for a bioavailability of tranexamic acid of greater than 40%, from about 41% to about 60%, preferably from about 42% to about 50%, more preferably about 45% after oral administration to humans.

In certain embodiments, the present invention is further directed to a modified release oral dosage form comprising from about 585 to about 715 mg of tranexamic acid or pharmaceutically acceptable salt thereof, preferably about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof, and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis.

In certain embodiments, the present invention is directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis, the dosage form providing a reduction of at least one side effect selected from the group consisting of headache, nausea, vomiting, diarrhea, constipation, cramping, bloating, and combinations thereof, as compared to an equivalent amount of tranexamic acid or pharmaceutically acceptable salt thereof in an immediate release oral dosage form when administered across a patient population.

In certain embodiments, the present invention is directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release excipient, said dosage form providing for the release of the tranexamic acid or pharmaceutically acceptable salt thereof which is slower than an immediate release oral dosage form and faster than a controlled release oral dosage form, such that the modified release oral dosage form is suitable for administration two or three times a day.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, the dosage form being suitable for oral administration on a three times a day basis, and the dosage form providing a mean maximum plasma concentration (C_{max}) of tranexamic acid of from about 5 to about 17.5 mcg/ml, preferably from about 6.5 to about 15 mcg/ml, more preferably from about 9 to about 14.5 mcg/ml per 1300 mg tranexamic acid after single dose oral administration to humans.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, the dosage form being suitable for oral administration on a twice a day basis, and the dosage form providing a mean maximum plasma concentration (C_{max}) of tranexamic acid of from about 5 to about 40 mcg/ml, preferably from about 10 to about 30 mcg/ml per 1950 mg tranexamic acid after single dose oral administration to humans.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, the dosage form

being suitable for oral administration on a three times a day basis, and the dosage form providing a mean plasma concentration of tranexamic acid of from about 5 to about 25 mcg/ml, preferably from about 7.5 to about 15 mcg/ml, more preferably from about 8 to about 10 mcg/ml, most preferably about 9 mcg/ml per 1300 mg tranexamic acid after steady state oral administration to humans.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, the dosage form being suitable for administration on a three times a day basis, and the dosage form providing a mean maximum plasma concentration (C_{max}) of tranexamic acid of from about 5 to about 25 mcg/ml, preferably from about 10 to about 20 mcg/ml, more preferably from about 12.5 to about 17.5 mcg/ml, most preferably about 15 to about 17 mcg/ml per 1300 mg tranexamic acid after steady state oral administration to humans.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and an modified release material, the dosage form being suitable for administration on a three times a day basis, and the dosage form providing a mean plasma trough concentration of tranexamic acid or pharmaceutically acceptable salt thereof of from about 2 to about 10 mcg/ml, preferably from about 3 to about 7.5 mcg/ml, more preferably about 4 to about 7 mcg/ml, most preferably about 5 to about 6 mcg/ml per 1300 mg tranexamic acid or after steady state oral administration to humans.

In certain embodiments, the invention is further directed to a method of treating a patient with a therapeutically effective amount of tranexamic acid or pharmaceutically acceptable salt thereof comprising administering to the patient two dosage forms of the present invention, each dosage form comprising from about 585 mg to about 715 mg of tranexamic acid or pharmaceutically acceptable salt thereof, preferably about 650 mg tranexamic acid or pharmaceutically acceptable salt thereof, and a modified release material such that the dosage form is suitable for oral administration on a three times a day basis.

In certain embodiments, the invention is further directed to a method of treating a patient with a therapeutically effective amount of tranexamic acid or pharmaceutically acceptable salt thereof comprising administering to the patient three dosage forms of the present invention, each dosage form comprising from about 585 mg to about 715 mg, preferably about 650 mg tranexamic acid or pharmaceutically acceptable salt thereof, and a modified release material such that the dosage form is suitable for oral administration on a twice a day basis.

In certain embodiments, the invention is directed to a dose of tranexamic acid or pharmaceutically acceptable salt thereof comprising two unit dosage forms of a modified release formulation, each unit dosage form of said modified release formulation comprising from about 585 mg to about 715 mg, preferably about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof, and a modified release material which provides for the release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dose provides a therapeutic effect when administered three times a day.

In certain embodiments, the invention is directed to a dose of tranexamic acid comprising three unit dosage forms of a modified release formulation, each unit dosage form of said modified release formulation comprising from about 585 mg to about 715 mg, preferably about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof, and a modified release material which provides for the release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dose provides a therapeutic effect when administered twice a day.

In certain preferred embodiments, the invention is further directed to a modified release oral dosage form including tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides a dissolution release rate in-vitro of the tranexamic acid or pharmaceutically acceptable salt thereof when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. of about 0% to about 40% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, from about 20% to about 60% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 30 minutes, from about 40% to about 80% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, from about 50% to about 95% by weight tranexamic acid or pharmaceutically acceptable salt thereof release at about 60 minutes, and not less than about 60% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes.

In certain preferred embodiments, the invention is further directed to a modified release oral dosage form including tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides a dissolution release rate in-vitro of the tranexamic acid or pharmaceutically acceptable salt thereof when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. of about 14% to about 22% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, from about 32% to about 50% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 30 minutes, from about 47% to about 71% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, from about 61% to about 92% by weight tranexamic acid or pharmaceutically acceptable salt thereof release at about 60 minutes, and from about 79% to about 100% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes.

In certain embodiments, the invention is directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and an effective amount of a modified release excipient such that the dosage form releases from about 10% to about 25% by weight tranexamic acid or pharmaceutically acceptable salt thereof every 15 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. In certain preferred embodiments, the dosage form releases about 18% to about 23% by weight tranexamic acid or pharmaceutically acceptable salt thereof every 15 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. Most preferably, the dosage form releases about 100% of said tranexamic acid or pharmaceutically acceptable

salt thereof within about 120 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. In certain embodiments, the dosage form releases about 1% of said tranexamic acid or pharmaceutically acceptable salt thereof every minute when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C.

In certain preferred embodiments, the modified release oral dosage form of the invention further provides a mean transit time of said tranexamic acid of 7.70±0.72 hours when administered across a patient population.

In certain preferred embodiments, the modified release oral dosage form of the invention further provides a mean absorption time of said tranexamic acid of 4.18±0.70 hours when administered across a patient population.

In certain further embodiments, the modified release oral dosage form of the present invention provides confidence intervals derived from ln-transformed pharmacokinetic kinetic parameters AUC_{0-t}, AUC_{inf} and C_{max} for tranexamic acid in plasma which are within a 80-125% range of an immediate release formulation including an equivalent amount of tranexamic acid when administered across a patient population under fasted conditions.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides less than about 20 percent incidence of headache as a side effect after single dose oral administration across a patient population.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides less than about 10 percent incidence of nausea as a side effect when administered across a patient population, less than about 7 percent incidence of nausea when administered across a patient population, preferable less than about 5 percent incidence of nausea as a side effect when administered across a patient population, more preferably less than about 2 percent incidence of nausea as a side effect after single dose oral administration across a patient population.

In certain embodiments, the modified release oral dosage form of the present invention provides less CNS side effects (e.g., headache), less GI side effects (e.g., nausea), or combination thereof in comparison to an equivalent amount of tranexamic acid or pharmaceutically acceptable salt thereof in an immediate release formulation when administered across a patient population. Additionally or alternatively, in certain embodiments the dosage form provides less CNS side effects (e.g., headache), less GI side effects (e.g., nausea), or combination thereof in comparison to a therapeutically equivalent amount of tranexamic acid administered intravenously in five minutes or less across a patient population.

In certain embodiments, the modified release oral dosage form of the present invention provides for the reduction of at least one side effect as compared to an immediate release oral dosage form including an equivalent amount of tranexamic acid or pharmaceutically acceptable salt thereof, when the immediate release dosage form is administered across a same or different population of patients as said modified release dosage form, and wherein said immediate release dosage form releases all of said tranexamic acid or pharmaceutically acceptable salt thereof within about 45 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. Such side effects can be for example, headache, nausea, vomiting, diarrhea, constipation, cramping, bloating, and combinations thereof.

In certain embodiments, the modified release oral dosage form of the present invention provides a mean transit time of tranexamic acid which is at least about 20 minutes longer, preferably about 30 minutes longer, than an immediate release formulation including an equivalent amount of tranexamic acid when administered across a patient population.

In certain embodiments, the dosage form of the present invention provides a mean absorption time of tranexamic acid which is at least about 20 minutes longer, preferably about 30 minutes longer, than an immediate release formulation including an equivalent amount of tranexamic acid when administered across a patient population.

In certain preferred embodiments, the therapeutically effective dose of the tranexamic acid or pharmaceutically acceptable salt thereof is provided via the administration of two or more dosage units. For example, if the dosage unit comprises 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and the dose for administration is about 1300 mg then two dosage units would be administered to a patient in need of such treatment, or for example, when the dose for administration is 1950 mg, three dosage units would be administered.

In certain preferred embodiments, the invention is further directed to a method of treating a patient with one or more modified release oral dosage forms comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, wherein the oral dosage form provides a therapeutically effective plasma level of tranexamic acid or pharmaceutically acceptable salt thereof in accordance with a three times a day (TID) dosing schedule, and the therapeutically effective dose administered comprises about 1300 mg of tranexamic acid or pharmaceutically acceptable salt thereof.

In certain preferred embodiments, the invention is further directed to a method of treating a patient with one or more modified release oral dosage forms comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, wherein the oral dosage form provides a therapeutically effective plasma level of tranexamic acid or pharmaceutically acceptable salt thereof in accordance with a twice a day (BID) dosing schedule, and the therapeutically effective dose administered comprises about 1950 mg of tranexamic acid or pharmaceutically acceptable salt thereof.

In certain embodiments, the invention is directed to a method of providing a tranexamic acid plasma concentration within the range of about 5 mcg/mL to about 15 mcg/mL by administration of a modified release formulation of the present invention comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material on a three times a day basis to a patient in need of tranexamic acid or pharmaceutically acceptable salt thereof treatment.

In certain embodiments, the invention is further directed to a method of treating a human patient with heavy menstrual bleeding (e.g., menorrhagia) comprising administering about 1300 mg of tranexamic acid or pharmaceutically acceptable salt thereof on a three times a day basis to the human patient to provide a tranexamic acid or pharmaceutically acceptable

salt thereof plasma concentration within the range of about 5 mcg/mL to about 15 mcg/mL after steady state oral administration to a human patient.

In certain embodiments, the invention is directed to a method of treating a patient suffering from menorrhagia, including patients with heavy menstrual bleeding due to fibroids, conization of the cervix, epistaxis, hyphema, hereditary angioneurotic edema, a patient with a blood coagulation disorder undergoing dental surgery, combinations thereof, and the like, by administering at least one dosage form of the present invention to the patient in need in tranexamic acid or pharmaceutically acceptable salt thereof therapy.

In certain embodiments, the invention is directed to a method of treating heavy menstrual bleeding with a therapeutically effective dose of at least one oral formulation of the present invention comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material wherein the menstrual blood loss per menstrual cycle is reduced by at least about 10 ml, preferably at least about 20 ml, more preferably at least about 40 ml. In a most preferred embodiment the menstrual blood loss per menstrual cycle is reduced by greater than or equal to about 50 ml.

In certain embodiments, the invention is directed to a method of treating heavy menstrual bleeding with a therapeutically effective dose of at least one oral formulation of the present invention comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which upon oral administration to a human female reduces the blood loss per menstrual cycle by about 35 ml to about 200 ml, preferably about 40 ml to about 175 ml, more preferably from about 50 ml to about 150 ml.

In certain embodiments, the invention is further directed to a method of treating heavy menstrual bleeding with a therapeutically effective dose of at least one oral formulation of the present invention comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which upon oral administration to a human female reduces the blood loss per menstrual cycle by about 20% to 100%, preferably from about 20% to about 70%.

In certain other embodiments, the present invention is directed to the use of the tranexamic acid formulations described herein for the treatment of heavy menstrual bleeding (menorrhagia) and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure, and physical activities.

The menstrual blood loss can be measured by procedures known in the art. For example, in certain embodiments, the menstrual blood loss can be determined by a procedure described by (i) L. Hallbert, et al. in "Determination of Menstrual Blood Loss", *Scandinav. J. Clin. & Lab. Investigation,* 244-248, 16, 1964, wherein the procedure is performed by extracting the menstrual blood from vaginal tampons and towels with a sodium hydroxide solution, converting heme chromogens to alkaline hematin, which is determined spectrophotometrically; or (ii) the menstrual blood loss can be determined by a procedure described by J. Newton, M. D., et al., in "A Rapid Method for Measuring Menstrual Blood Loss Using Automatic Extraction.", *Contraception,* 269-282, September 1977, Vol. 16, No. 3, wherein the procedure is based upon the formation of alkaline haematin after the blood has been extracted from vaginal tampons and sanitary towels by an automatic Stomacher Lab-Blender. The disclosures of the aforementioned articles are hereby incorporated by reference in their entireties.

In certain embodiments, the modified release material may be incorporated in a coating applied onto e.g., a tablet comprising the tranexamic acid or pharmaceutically acceptable salt thereof, or may be incorporated into a matrix with the tranexamic acid or pharmaceutically acceptable salt thereof, or a combination thereof. For example, in certain preferred embodiments, the modified release material is a controlled release material such as a gel-forming or hydratable polymer which is added to e.g., a matrix composition comprising the tranexamic acid or pharmaceutically acceptable salt thereof.

In certain embodiments, the tranexamic acid for use in the methods and formulations of the present invention is in the form of a pharmaceutically acceptable salt thereof. Such salt forms include for example and without limitation the sodium salt, potassium salt, calcium salt, magnesium salt and the like; as well as the hydrochloride, hydrobromide, sulfate, phosphate, formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate-methanesulfonate salt forms, and the like. Preferably the active ingredient for use in accordance with the present invention is tranexamic acid.

An "immediate release oral dosage form" for purposes of the present invention is a dosage form which releases all of active ingredient (e.g., tranexamic acid) included therein within about 45 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C.

A "modified release oral dosage form" for purposes of the present invention is an oral dosage form which releases the active ingredient (e.g., tranexamic acid) included therein in a manner that is slower than an immediate release oral dosage form and faster than a controlled release oral dosage form, when the dosage forms include the same amount of active as the modified release oral dosage form. One definition of the terms "slower" and "faster" as used in this application is that they are meant to represent a statistically significant difference at each measured 15 minute interval after the start of in-vitro dissolution. In certain preferred embodiments, the modified release oral dosage form of the present invention provides an in-vitro dissolution release rate of tranexamic acid or pharmaceutically acceptable salt thereof, when measured by a USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C., of less than about 70% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes and about 100% by weight of said tranexamic acid or pharmaceutically acceptable salt thereof released by about 120 minutes.

A "controlled release oral dosage form" for purposes of the present invention is a dosage form which releases all of the active ingredient (e.g., tranexamic acid) included therein after about 4 hours or more when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C.

The term "C_{max}" unless otherwise indicated is meant for purposes of the present invention to mean the maximum plasma concentration of a medicament achieved after single dose administration of a dosage form, or the maximum plasma concentration of a medicament achieved over a dosing interval from multiple-doses at steady-state in accordance with the present invention.

The term "T_{max}" is meant for purposes of the present invention to mean the elapsed time from administration of a dosage form to the time the C_{max} of the medicament is achieved.

The term "steady state" means that the amount of the drug reaching the system is approximately the same as the amount of the drug leaving the system. Thus, at "steady-state", the patient's body eliminates the drug at approximately the same rate that the drug becomes available to the patient's system through absorption into the blood stream.

The term "mean" for purposes of the present invention, when used to define a pharmacokinetic value (e.g., T_{max}), unless specified otherwise, represents the arithmetic mean value measured across a patient or subject population.

The term "three times a day (TID) basis" for purposes of the present invention, means that the dosage regimen is to be administered three times a day, preferably on a schedule of every 8 hours.

The term "mean transit time" is understood by those skilled in the art and means the time-point where 63.2% of the total AUC is attained after oral administration, or 63.2% of the IV dose is eliminated, as described in *Applied Pharmacokinetics, Principles of Therapeutic Drug Monitoring*, Second Edition (1986), edited by William E. Evans, et al., the disclosure of which is hereby incorporated by reference in its entirety.

The term "mean absorption time" is understood by those skilled in the art and means a quantitative parameter which summarizes how long, on average, the drug molecule remains unabsorbed, i.e. persists in its dosage form and in the gastrointestinal tract, also as described in *Applied Pharmacokinetics, Principles of Therapeutic Drug Monitoring*, Second Edition (1986), edited by William E. Evans, et al. Unlike the absorption rate constants (ka) which can be skewed, the mean absorption time is not affected by incomplete release of drug from its dosage form, irregular absorption, lag-time, mixed zero-order dissolution rates, changing GI motility, GI blood flow, first-pass effect, etc.

"Therapy" for excessive menstrual bleeding is defined for the purpose of this invention as one or more courses of treatment with an antifibrinolytic agent such as, but not limited to, tranexamic acid, aminocaproic acid, and any pharmaceutically acceptable salts, esters, derivatives, pro-drugs, metabolites, and analogues of any of the foregoing antifibrinolytic agents.

The term "heavy menstrual bleeding" is defined for purposes of the present invention as a perceived blood loss of at least heavy to very heavy which may correspond to a periodic blood loss of at least about 30 ml per cycle to as much as 1000 ml per cycle as measured by the alkaline hematin test. The periodic blood loss perceived or as measured with the alkaline hematin test may vary depending on the severity of the condition and the physiological make up of the individual patient. Therefore, heavy menstrual bleeding may include periodic blood losses of at least about 30 ml per cycle. Losses from between about 30 ml, about 40 ml, about 50 ml, about 60 ml, about 70 ml, about 80 ml, about 90 ml to about 300 ml are contemplated as are losses greater than 300 ml, such as for example, losses between about 300 ml to about 1000 ml.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** depicts concentration-time profiles for simulated administration of the 1.3 g tranexamic acid modified release formulation of Example 1 at a Q8H (every 8 hours) dosing schedule of 6:00 AM, 2:00 PM, 10:00 PM comparing it with 1 g administered Q8H.

FIG. **2** depicts concentration-time profiles for simulated administration of the 1.3 g tranexamic acid modified release formulation of Example 1 at a TID (three times a day) dosing schedule of 8:00 AM, 2:00 PM, 8:00 PM comparing it with 1 g administered TID.

FIG. **3** depicts mean plasma concentration-time profiles on a semi-log scale over 36 hours for the study of Example 4.

FIG. **4** depicts mean plasma concentration-time profiles on a linear scale over 36 hours for the study of Example 4.

FIG. **5** depicts the dissolution profiles of the modified release tranexamic acid formulation of Example 1; the immediate release tranexamic acid formulation of Example 2; the delayed release tranexamic acid formulation of Example 3A, and the commercial Cyklokapron immediate release formulation of Example 4A.

FIG. **6** depicts the dissolution profile of all of the exhibit batches of the modified release tranexamic acid formulations of the present invention and the commercial Cyklokapron immediate release formulation of Example 4A.

FIG. **7** is a listing of the Menorrhagia Impact Measures of the present invention.

FIG. **8** is a graph of Menorrhagia Instrument measure #1 percentage of patients and normals indicating each response at baseline (BL) and at one (1) month (M1).

FIG. **9** is a graph of the limitations of social and leisure activities (LSLA) in women with Heavy Menstrual Bleeding (HMB) in accordance with the treatment regimens administered in Examples 8 and 9.

FIG. **10** is a graph of the mean menstrual blood loss change from the clinical studies of Examples 8 and 9.

DETAILED DESCRIPTION

The tranexamic acid (API) utilized in the formulations of the present invention is available from various manufacturers. The tranexamic acid particles utilized in the present invention may range from about 0.1 to about 550 microns. For example, the tranexamic acid particles may have a particle size range from <about 0.5 to about 520 microns.

The tranexamic acid particles utilized in the present invention may have a D_{25} particle size distribution ranging from about 5 to about 15 microns, a D_{50} particle size distribution ranging from about 14 to about 73 microns, and a D_{75} particle size distribution ranging from about 30 to about 205 microns.

The particle size of the tranexamic acid utilized may also have a particle size range wherein about 1% of the particles are of a size greater than about 250 microns, about 8% of the particles are of a size of about 180 microns, about 9% of the particles are of a size of about 150 microns, about 4% of the particles are of a size of about 125 microns, about 20% of the particles are of a size of about 75 microns, about 14% of the particles are of a particle size of about 45 microns, and about 44% of the particles are of a particle size less than about 45 microns.

The tranexamic acid utilized may also have a particle size range wherein about 5% of the particles are of a size greater than about 250 microns, about 12% of the particles are of a size of about 180 microns, about 14% of the particles are of a size of about 150 microns, about 14% of the particles are of a size of about 125 microns, about 29% of the particles are of a size of about 75 microns, about 12% of the particles are of a particle size of about 45 microns, and about 14% of the particles are of a particle size less than about 45 microns.

The tranexamic acid utilized may also have a particle size range wherein about 2% of the particles are of a size greater than about 250 microns, about 7% of the particles are of a size of about 180 microns, about 9% of the particles are of a size of about 150 microns, about 4% of the particles are of a size of about 125 microns, about 20.5% of the particles are of a size of about 75 microns, about 16% of the particles are of a particle size of about 45 microns, and about 41.5% of the particles are of a particle size less than about 45 microns.

The tranexamic acid utilized may also have a particle size range wherein about 0% of the particles are of a size greater than about 250 microns, about 5% of the particles are of a size of about 180 microns, about 12% of the particles are of a size of about 150 microns, about 11% of the particles are of a size of about 125 microns, about 31% of the particles are of a size

of about 75 microns, about 17% of the particles are of a particle size of about 45 microns, and about 24% of the particles are of a particle size less than about 45 microns.

The tranexamic acid utilized may also have a particle size range wherein about 20% of the particles are of a size of about 125 microns, about 20% of the particles are of a size of about 75 microns, about 20% of the particles are of a particle size of about 45 microns, and about 45% of the particles are of a particle size less than about 45 microns.

The dosage regimen typically listed for tranexamic acid in HMB (Heavy Menstrual Bleeding) therapy is 1-1.5 g per dose administered three-four times a day at the onset of copious menstrual bleeding and continued for the first 3-5 days of the menstrual cycle. However, the most frequently reported dosage regimen of tranexamic acid is an immediate release oral formulation in which 1 g tranexamic acid is administered four times a day (4 g per day) for HMB therapy outside of the US. Knowledge of this common regimen is supported by a careful review of the randomized controlled trials published in the medical literature, product labeling from other countries' regulatory authorities having the product approved for HMB therapy, utilization data from Sweden (Rybo 1991), correspondence and interviews with non-US clinicians having experience with the product. That regimen is currently the dosage being studied by the US Center for Disease Control (CDC) in women with HMB associated with bleeding disorders.

The absolute bioavailability of tranexamic acid observed when administering the European commercial formulation (Cyklokapron, Kabi AB, Sweden Batch 90288; assay 499 mgm/tablet) to male subjects is approximately 35% and its elimination correlates with renal creatinine clearance. Peak serum tranexamic acid concentrations occur approximately 3 hours after the oral administration of a European immediate-release tablet formulation (>85% dissolved at 15 minutes) (Pilbrant, et al., *Eur. J. Clin. Pharmacol*, (1981)-20:65-72). By comparison, the in vivo absorption profile observed with the European immediate-release formulation is slow and very gradual over 3 hours. Specifically, tranexamic acid serum concentrations are 9, 41, 73, 88 percent (with food), and 22, 63, 85, and 98 percent (fasting) of maximal absorption at 0.5, 1, 1.5 and 2 hours after a 2 g oral dose, respectively. Although not wishing to be held to any specific theory, it is presently hypothesized that tranexamic acid oral absorption appears to be controlled by a non-dissolution rate limited process; i.e. the rate and extent of oral absorption is a function of a transmembrane passage-limited process, in order to explain the disparity between the time of product dissolution and relatively prolonged tmax (time to achieve the peak serum concentration).

Preferably, the goal of the formulation, dose strength and dosage regimen of the invention, is to provide HMB therapy which achieves from about 20% to 100% reduction in menstrual blood loss per menstrual cycle. In accordance with certain embodiments of the present invention, the preferred tranexamic acid dose of 1.3 g every 8 hours is predicted to provide an average serum tranexamic acid concentration comparable to that produced by a 1 g every 6 hour regimen (i.e. 12.4 mcg/mL), with associated peaks and troughs falling approximately within the therapeutic antifibrinolytic range (5-15 mcg/mL; Cyklokapron NDA 19-280). In certain embodiments, a two-compartment oral absorption and elimination simulation model coupled with pharmacokinetic data (Pilbrant, et al., *Eur. J. Clin. Pharmacol*, (1981)-20:65-72), and modified-release tablet dissolution performance information were used to determine the preferred lead dosage regimen.

In immediate release formulations the entire dose and the soluble components in the dosage form dissolve in gastrointestinal fluid and present a high concentration of solutes for absorption. The most frequently reported adverse effects are primarily confined to the proximal gastrointestinal tract (nausea and vomiting). These adverse symptoms appear to be related to the drug load presented to the gastric mucosa, since this effect can be minimized by reducing the immediate-release oral formulation dose or administering the product slowly by the intravenous route. In certain embodiments, a lower incidence of proximal gastrointestinal adverse effects is obtained with the preferred oral modified release formulation (e.g., dosed 1.3 g every 8 hours) of the invention, e.g., because of the modified release properties of the drug product formulation.

In certain embodiments, the oral dosage form of the present invention provides for an increased bioavailability as compared to immediate release oral dosage forms currently available (e.g., Cyclokapron). In certain preferred embodiments the increased bioavailability allows therapeutic plasma levels of tranexamic acid to be reached with a lower dose of drug. Preferably, the increased bioavailability also decreases the amount of tranexamic acid that remains unabsorbed in the gastrointestinal which leads to decreased incidence of side effects that are typically associated with formulations that provide higher levels of unabsorbed tranexamic acid and prolonged exposure of the gastrointestinal tract to the higher tranexamic acid levels. Preferably the oral dosage form of the present invention provides for a bioavailability of tranexamic acid of greater than 40%, from about 41% to about 60%, preferably from about 42% to about 50%, more preferably about 45% after oral administration to humans.

The modified release oral formulations of tranexamic acid of the present invention provides a release of the drug which is slower than that of the immediate release 500 mg Cyklokapron product current marketed in Canada which provided a mean release rate of 100% by weight tranexamic acid released by about 15 minutes when measured utilizing USP 27 Apparatus Type II paddle method @ 50 RPM in 900 ml water at 37±0.5° C.

In certain embodiments, the modified release oral formulations may be described as providing a mean transit time through the proximal gastrointestinal mucosa which takes approximately one half hour longer than an immediate release formulation. In other preferred embodiments, the modified release formulations of the invention provide a rate of release of (dissolved) tranexamic acid from the dosage form in-vitro which is approximately 20, 40, 60, 80, and 100 percent of the total dose at 0.25, 0.5, 0.75, 1 and 1.5 hours, respectively. In certain preferred embodiments, such a release rate in-vitro demonstrates that the formulations of the present invention provide a relative reduction in the amount and rate of dissolved tranexamic acid presented to the proximal gastric mucosa to approximate 20, 40, 60, 80, and 100 percent of the total dose at 0.25, 0.5, 0.75, 1 and 1.5 hours, respectively, after oral administration.

In certain embodiments, the majority of tranexamic acid absorption appears to occur slowly distal to the stomach, and assuming linear pharmacokinetics, the modified release formulation produces an absorption profile which is comparable to that achieved with the currently available oral immediate release formulations used outside the U.S.

In accordance with the present invention a modified release tranexamic acid tablet for oral administration is disclosed. Preferably, the tablet contains at least one material (defined herein as any substance other than the active, i.e., tranexamic acid) which minimizes or eliminates the adverse gastrointes-

tinal side effects in patients, for example, women dosed with oral tranexamic acid for treatment of menorrhagia.

The modified release oral dosage forms of tranexamic acid for purposes of the present invention include formulation ingredients and/or configurations which are typically utilized for formulations known in the art as extended, sustained and controlled release formulations, although modified to provide a desirable release rate in keeping with the teachings of the present invention. The modified release formulations preferably decrease the concentration of tranexamic acid and materials dissolved in the stomach fluids after dosing by controllably releasing tranexamic acid over a period of time, as opposed to immediate release formulations which release the entire dose of tranexamic acid all at once. The modified release formulations of the present invention thus minimize or prevent gastrointestinal reactions and side effects that occur when a dose of tranexamic acid is ingested and immediately reaches the stomach.

The modified release dosage forms of the present invention may be prepared as; tablets, capsules, granules, pellets, powders, dragees, troches, non-pariels, pills or encapsulated suspension, and may be packaged into capsules, sachets, etc. Such dosage forms may be prepared by any formulation technique where release of the active substance (tranexamic acid) from the dosage form is modified to occur at a slower rate than from an immediate release product. In these formulations, tranexamic acid release occurs in the stomach and/or intestine, but at a slower rate so that a bolus of dissolved drug does not reach the lining of the stomach and cause adverse effects, or adverse effects occur with a lower intensity or frequency because of the lower concentration of tranexamic acid. Hence, adverse effects are preferably reduced, minimized or eliminated.

Methods of preparing modified release formulations are found in Modified Release Drug Delivery Technology, Rathbone, Hadgraft, and Roberts, Eds., Drugs and the Pharmaceutical Sciences, Vol. 126, Marcel Dekker Inc., New York, 2003; Modern Pharmaceutics, Third Edition, Banker and Rhodes, Eds. Drugs and the Pharmaceutical Sciences, Vol. 72, Marcel Dekker Inc., New York, 1996; Sustained and Controlled Release Drug Delivery Systems, Robinson, Ed., Drugs and the Pharmaceutical Sciences, Vol. 6, Marcel Dekker Inc., NY 1978; Sustained Release Medications, Chemical Technology Review No. 177, Johnson, Ed., Noyes Data Corporation 1980; Controlled Drug Delivery, Fundamentals and Applications, Second Edition, Robinson and Lee, Eds., Marcel Dekker Inc., New York, 1987, and as described in U.S. Pat. No. 6,548,084, each of these references being expressly incorporated by reference herein in its entirety.

Preferably, a modified release form, makes tranexamic acid available over an extended period of time after ingestion. Modified release dosage forms coupled with the digestion process and the absorption process in the gastrointestinal tract cause a reduction in the amount of tranexamic acid in solution in the gastrointestinal tract compared to dosing tranexamic acid presented as a conventional dosage form (e.g., as a solution, or as an immediate release dosage form). The modified release formulation may be verified by in vitro dissolution testing and in vivo bioequivalence documentation, according to Food and Drug Administration standards, e.g., as set forth at www.fda.gov, 21 CFR §314, 320, and also at USP 23 NF 18 §711, 724. For example, an in vitro dissolution test such as USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. may be used to verify the release of the tranexamic acid from the dosage form.

Tranexamic acid modified release tablets may be formulated to provide a dose of tranexamic acid, typically about 500 mg to about 2 grams from one to two tablets, within about the first one to two hours after the tablet is ingested. Thus, tranexamic acid release occurs at a designed rate over a period e.g., about 60 minutes to about 120 minutes. The rate of tranexamic acid release over this period of time is designed to provide a reduced concentration of tranexamic acid in the stomach while allowing the absorption of tranexamic acid to occur throughout the gastrointestinal tract. Absorption of tranexamic acid typically begins as soon as tranexamic acid is released from the dosage form and is dissolved in the gastrointestinal fluids contacting the membranes which line the gastrointestinal tract. The rate of release of tranexamic acid from the dosage form and the absorption of drug by the gastrointestinal mucosa help to maintain low concentrations of drug in the gastrointestinal fluids. The lowered concentrations preferably result in lower intensity, frequency, and/or severity of gastrointestinal adverse side effects. The designed rate of release of tranexamic acid from the dosage form in the stomach and the upper small intestine, the natural emptying of gastric juice containing any dissolved tranexamic acid from the stomach, and the absorption of tranexamic acid from a larger segment of the gastrointestinal tract (i.e., both the stomach and the small intestine, rather than the stomach only or the lower portion of the small intestine if any modified release dosage form with a longer release time was used), preferably results in reduced levels of dissolved tranexamic acid in the region of the gastrointestinal tract proximal or distal to the dosage form. Reduced concentrations of tranexamic acid along the gastrointestinal tract preferably provide a reduction in adverse gastrointestinal effects associated with oral tranexamic acid therapy.

As used herein, alleviation of adverse effects using these formulations indicates any relief in one or more symptoms, such as decrease in incidence, severity, or duration of symptoms, and is not limited to absence of symptoms or elimination of symptoms. Thus, treatment includes any decrease in incidence, duration, intensity, frequency, etc. of adverse gastrointestinal symptoms including, but not limited to, headache, nausea, vomiting, diarrhea, constipation, cramping, bloating, and combinations thereof. The formulations may reduce symptoms at any time during tranexamic acid therapy, but minimized adverse effects are particularly noted immediately or shortly after dosing, that is, within the first few hours after dosing. As used herein, adverse gastrointestinal effects and side effects are used interchangeably to indicate nontherapeutic effects (i.e., not relating to any possible beneficial effects due to tranexamic acid), ranging from unpleasant but tolerable sensations to severe gastrointestinal symptoms. As used herein, the terms oral formulations, ingestable formulations, and orally administered formulations are used interchangeably and include any dosage forms which are ingested by mouth, including, but not limited to, tablets, pills, liquids, gelcaps, softgels, dragees, capsules, powders, granules, pellets, etc.

Modified release formulations of tranexamic acid include tablets, pellets, granules, capsules, or other oral dosage forms prepared in such a way to release tranexamic acid in a designed manner. In certain embodiments, the modified release material is a gel-forming polymer, a hydratable polymer, a water soluble polymer, a water swellable polymer, or mixtures thereof.

In certain embodiments, modified release tranexamic acid tablets are prepared by adding a modified release material comprising a gel-forming or hydratable polymer to a tranexamic tablet composition. Suitable gel-forming or hydratable polymers include, but are not limited to, hydroxyproplycellulose, hydroxypropylmethylcellulose or hypromellose, car-

boxymethylcellulose, polyvinyl alcohol, etc. This provides a compressed tablet that may or may not be film coated. The tablet releases tranexamic acid by diffusion of tranexamic acid through the tablet matrix, or by erosion of the tablet matrix, or by a combination of diffusion from and erosion of the tablet matrix. Tablets formed with water swellable polymers release tranexamic acid by diffusion of tranexamic acid through the tablet matrix, or by erosion of the tablet matrix, or by a combination of diffusion from and erosion of the tablet matrix. One or more water-soluble hydrophilic polymer(s) may also be used. These include polyvinyl pyrrolidine, hydroxypropyl cellulose, hydroxypropylmethylcellulose, now referred to as hypromellose (e.g., Methocel™, Dow Chemical Company), methyl cellulose, vinyl acetate/crotonic acid copolymers, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers, derivatives thereof and mixtures thereof. In various embodiments, the polymer is hydroxypropyl cellulose or hydroxypropylmethylcellulose. The polymer may be hydroxypropyl-methyl cellulose with a viscosity ranging from about 50 cps to about 200 cps. The polymer may be hydroxypropyl-methyl cellulose with a viscosity of 100 cps, commercially available as Methocel™ K 100 LV (Dow Chemical Company). The amount of polymer in the composition may be in the range of about 5% by weight to about 50% by weight of the composition. In various embodiments, the polymer is in the range of about 10% by weight to about 35% by weight of the composition, or about 10% by weight to about 30% by weight of the composition.

In certain embodiments the modified release material comprises a vinyl polymer, phthalic acid derivative of vinyl copolymer, hydroxyalkylcellulose, alkylcellulose (e.g., ethylcellulose), cellulose acetate, hydroxyalkylcellulose acetate, cellulose ether, alkylcellulose acetate and partial esters thereof, and polymers and copolymers of lower alkyl acrylic acids and lower alkyl acrylates and partial esters thereof, or combination thereof. In preferred embodiments the modified release material comprises hydroxypropylcellulose, hydryoxpropylmethylcellulose, carboxymethylcellulose, polyvinyl alcohol, polyvinylpyrrolidone, methylcellulose, vinyl acetate/crotonic acid copolymers, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers, derivatives thereof, and mixtures thereof. In further preferred embodiments the modified release material comprises a polymer such as a methacrylic acid copolymer. These are copolymers of methacrylic acid with neutral acrylate or methacrylate esters such as ethyl acrylate or methyl methacrylate.

In certain embodiments the modified release material comprises a pH independent binder or film-forming agent such as hydroxypropyl methycellulose, hydroxypropyl cellulose, methylcellulose, polyvinylpyrrolidone, neutral poly(meth) acrylate esters (e.g., the methyl methacrylate/ethyl acrylate copolymers sold as Eudragit® (Rohm Pharma), starches, gelatin, sugars such as glucose, sucrose, and mannitol, silicic acid, carboxymethylcellulose, and the like, diluents such as lactose, mannitol, dry starch, microcrystalline cellulose and the like, surface active agents such as polyoxyethylene sorbitan esters, sorbitan ethers, and the like, coloring agents, flavoring agents, lubricants such as talc, calcium stearate, and magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and other tableting aids. Any combination of the aforementioned binders or film-forming agents may be included in the modified release material. The modified release material may be combined with tranexamic acid to form modified release dosage forms.

In certain embodiments, the formulation includes tranexamic acid in the range of about 50% by weight to about 95% or more by weight of the formulation. In other embodiments, tranexamic acid is in the range of about 60% by weight to about 90% by weight, or about 60% by weight to about 80% by weight of the formulation. The remaining weight may be made up of the modified release material and additional excipients.

To prepare modified release tablet formulations, the agent or modified release material to slow the release of tranexamic acid may be incorporated into the tablet matrix or coated onto the tablet surface or both. In certain embodiments, tablet formulations prepared are formulated by granulating a blend of powders of the modified release material. The powder blend is formed by combining portions of the powdered components that make up the tablet. These powders are intimately mixed by dry-blending. The dry blended mixture is granulated by wet mixing of a solution of a binding agent with the powder blend. The time for such wet mixing may be controlled to influence the dissolution rate of the formulation. For example, the total powder mix time, that is, the time during which the powder is granulated, may range from about 1 min to about 10 min, or from about 2 min to about 5 min. Following granulation, the particles are removed from the granulator and placed in a fluid bed dryer, a vacuum dryer, a microwave dryer, or a tray dryer for drying. Drying conditions are sufficient to remove unwanted granulating solvent, typically water, or to reduce the amount of granulating solvent to an acceptable level. Drying conditions in a fluid bed dryer or tray dryer are typically about 50 to 70° C. The granulate is dried, screened, mixed with additional excipients such as disintegrating agents, flow agents, or compression aids and lubricants such as talc, stearic acid, or magnesium stearate, and compressed into tablets.

In certain embodiments, the tablet that contains a modified release material within the tablet matrix may be coated with an optional film-forming agent. This applied film may aid in identification, mask an unpleasant taste, allow desired colors and surface appearance, provide enhanced elegance, aid in swallowing, aid in enteric coating, etc. The amount of film-forming agent may be in the range of about 2% tablet weight to about 4% tablet weight. Suitable film-forming agents are known to one skilled in the art and include hydroxypropyl cellulose, cellulose ester, cellulose ether, one or more acrylic polymer(s), hydroxypropyl methylcellulose, cationic methacrylate copolymers (diethylaminoethyl)methacrylate/methyl-butyl-methacrylate copolymers such as Eudragit E® (Rohm Pharma) and the like. The film-forming agents may optionally contain colorants, plasticizers, fillers, etc. including, but not limited to, propylene glycol, sorbitan monooleate, sorbic acid, titanium dioxide, and one or more pharmaceutically acceptable dye(s).

In certain embodiments, the tranexamic acid tablets of the invention are coated with a modified release material. In certain embodiments, tranexamic acid tablets are formulated by dry blending, rotary compacting, or wet granulating powders composed of tranexamic acid and tablet excipients. These powders are compressed into an immediate release tablet. Coating this immediate release tablet with a modified release material as described herein renders this tranexamic acid tablet as a modified release tablet.

In addition to the modified release material, the formulations of the invention may also contain suitable quantities of other materials, e.g. preservatives, diluents (e.g., microcrystalline cellulose), lubricants (e.g., stearic acid, magnesium stearate, and the like), binders (e.g., povidone, starch, and the like), disintegrants (e.g, croscarmellose sodium, corn starch, and the like), glidants (e.g., talc, colloidal silicon dioxide, and the like), granulating aids, colorants, and flavorants that are conventional in the pharmaceutical art. Specific examples of

pharmaceutically acceptable excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (2003), incorporated by reference herein.

The release process may be adjusted by varying the type, amount, and the ratio of the ingredients to produce the desired dissolution profile, as known to one skilled in the art. A coating may be a partially neutralized pH-dependent binder that controls the rate of tranexamic acid dissolution in aqueous media across the range of pH in the stomach, which has a pH of about 2, and the intestine, which has a pH of about 5.5 in its upper region. In certain embodiments, one or more pH dependent binders may be used to modify the dissolution profile so that tranexamic acid is released slowly and continuously as the formulation passes through the stomach and/or intestines.

In one embodiment, compressed modified release tablets are formulated to comply with USP criteria and to be of such a size and shape to be easy to swallow. The size of the tablet will depend upon the dose of tranexamic acid that is needed to provide adequate therapy and the particular formulation and excipients that are selected to provide the physical properties necessary for tableting and for modified release. In various embodiments, a compressed modified release tablet contains from about 500 mg to about 1 gram of tranexamic acid, or from about 600 mg to about 750 mg of tranexamic acid. The daily dose of tranexamic acid may be achieved by taking one or two tablets at each dosing time.

In certain embodiments, the tranexamic acid included in the dosage form is from about 375 mg to about 1500 mg, preferably from about 375 mg to about 1000 mg. In one embodiment, the dose of tranexamic acid per tablet is in the range of about 500 mg to about 1000 mg for tablets and from about 500 mg to about 1500 mg for a sachet filled with granules. In another embodiment, the dose of tranexamic acid is in the range of about 3 grams/day to about 6 grams/day in three or four divided doses. As an example, a total daily dose of 3 grams tranexamic acid may be divided into three doses of one tablet each with each tablet containing 1 gram tranexamic acid, or may be divided into four doses of one tablet each with each tablet containing 0.75 gram tranexamic acid. As another example, a total daily dose of 4 gram tranexamic acid may be divided into three doses of two tablets at each dose with each tablet containing 0.666 gram tranexamic acid, or may be divided into four doses of one tablet each with each tablet containing 1 gram tranexamic acid. As another example, a total daily dose of 5 gram tranexamic acid may be divided into three doses of one tablet each with each tablet containing 1.66 gram tranexamic acid, or may be divided into four doses of two tablets each with each tablet containing 0.625 gram tranexamic acid. As another example, a total daily dose of 6 gram tranexamic acid may be divided into three doses of two tablets each with each tablet containing 1 gram tranexamic acid, or may be divided into four doses of two tablets each with each tablet containing 0.75 gram tranexamic acid. For ease of swallowing, the dose of tranexamic acid taken at each dosing time may be delivered by taking multiple tablets. For example, the 4 gram daily dose may be delivered by taking two 666.67 mg tablets three times a day or two 500 mg tablets four times a day. Similarly, the 3 gram daily dose may be achieved by taking two 550 mg tablets three times a day or two 375 mg tablets four times a day. Alternatively, for ease of reference, a dose of 600 mg, 650 mg, or 700 mg of tranexamic acid per tablet may be used. In a preferred embodiment, a total daily dose of 3900 mg/day is administered in three divided doses of 1300 mg of two tablets at each dose with each tablet containing 650 mg of tranexamic acid. Alternatively, each dose may be delivered by taking granules containing the prescribed amount of tranexamic acid presented in a convenient unit dose package. Such examples are not limiting and other doses within these ranges will be appreciated by those skilled in the art.

Since tranexamic acid is primarily eliminated via the kidneys by glomerular filtration with more than 95% excreted unchanged drug in the urine, dosage adjustment may be recommended. The table below lists some recommended dosage adjustments for renal impairment:

Dose Adjustment Table

Serum Creatinine (mg/dl)	Estimated GFR* (ml/min)	Adjusted dose	Total daily dose
1.4 to 2.8	30-60	1.3 g (two 650 mg tablets) BID	2.6 g
2.8 to 5.7	15-30	1.3 g (two 650 mg tablets) QD	1.3 g
>5.7	<15	1.3 g (two 650 mg tablets) every 48 hours or 650 mg (one tablet) every 24 hours	0.65 g

Alternatively, modified release tranexamic acid formulations may be administered by pellets or granules in e.g., a sachet or capsule. Modified release tranexamic acid pellets or granules may be prepared by using materials to modify the release of tranexamic acid from the granule or pellet matrix. Modified release preparations may also be formulated using coatings to modify the release of tranexamic acid from the granule or pellet. U.S. Pat. Nos. 5,650,174; and 5,229,135 each of which is expressly incorporated by reference herein in its entirety, disclose variations on fabricating a pellet or nonpareil dosage form. Spheres are filled into packets, termed sachets, or capsules which are filled by weight to contain the prescribed dose of drug. Multiparticulates may be coated with an modified release coating, as disclosed in U.S. Pat. No. 6,066,339, which is expressly incorporated by reference herein its entirety. Coated multiparticulates may be packaged in capsules or sachets. The formulation of granules or pellets for modified release is described in Multiparticulate Oral Drug Delivery, Ghebre-Sellassie, Ed. in Drugs and the Pharmaceutical Sciences, Vol. 65 Marcel Dekker Inc. NY, 1994 and in the relevant parts of the references for modified release formulations previously cited and the relevant portions incorporated herein by reference.

Additional tranexamic acid formulations are disclosed in U.S. patent application Ser. Nos. 10/631,371, filed Jul. 31, 2003; 12/220,241, filed Jul. 23, 2008; and 11/346,710, filed Feb. 3, 2006, the disclosures of which are hereby incorporated by reference in their entirety.

In certain embodiments, the inventive tranexamic acid formulations may be used for additional indications other than menorrhagia, such as conization of the cervix, epistaxis, hyphema, hereditary angioneurotic edema, a patient with a blood coagulation disorder undergoing dental surgery, combinations thereof, and the like.

Menorrhagia Instrument

With regard to the treatment of menorrhagia (Heavy Menstrual Bleeding) studies of the safety and efficacy of the antifibrinolytic tranexamic acid were conducted. As part of these studies a diagnosis and treatment instrument (Mnorrhagia Instrument; MI) was designed. The instrument reliably identifies and monitors heavy menstrual bleeding patients and can be used in conjunction with an antifibrinolytic agent to diagnose and monitor the treatment of heavy menstrual bleeding.

A Menorrhagia Instrument (MI) of the invention reliably captures the diagnosis and treatment of the disease by measuring the impact of treatment on the symptoms associated with heavy menstrual bleeding. The information obtained from individual patient responses to the measures described in the methods of the present invention correlates to blood loss as measured by the alkaline hematin test. For example, data from the measures of social, leisure and/or physical activity symptoms, correlate with the volume of blood loss, and the change in the intensity of these symptoms correlates with the change in volume of blood lost, thus providing a measurement for the successful diagnosis and evaluation of treatment of bleeding disorders.

The instrument of the present invention measures specific aspects of the patient's monthly menstrual period. The measures correlate with the diagnosis of heavy menstrual bleeding and with the course of antifibrinolytic treatment. Further each of the measures individually correlate with quantity of blood loss as measured by the alkaline Hematin test. The symptomatic measures include: 1) a functional assessment measure; and ii) a pharmacology (or therapy assessment) measure.

The functional assessment measure of symptoms is further factored into segments which include 1) a measure of functional impairment generally; 2) impairment of necessary activities; and 3) impairment of discretionary activities.

The pharmacology domain provides an assessment of the severity of the menstrual period.

Specific symptomatic measures may be directed to an initial patient assessment and to the treatment period (pharmacology measure). Examples of specific measures would include examples of initial patient assessment measures (measures 1-4 listed in the Menorrhagia Instrument of FIG. 7); and therapy assessment measures (measures 1-4 together with measures 6, 6a, 6b and 6c contained in the Menorrhagia Instrument of FIG. 7).

In certain embodiments, the present invention is directed to a method of diagnosing and treating heavy menstrual bleeding, wherein the initial diagnoses of heavy menstrual bleeding is accomplished by evaluation of the most recent menstrual period on the basis of one, some or all of the prescribed symptomatic measures of FIG. 7. Measures which may be used as part of the initial patient assessment include, for example: a) determining a patient's perceived blood loss during their most recent menstrual period; b) determining how much the patient's blood loss limited their work outside and inside the home; c) determining how much the patient's blood loss limited their physical activities; d) determining how much the patient's blood loss limited their social and leisure activities; and e) determining the specific activities that were limited by the patient's blood loss.

The assessment of the patient's perceived blood loss during their most recent menstrual period may include an inquiry such as "during your most recent menstrual period, your blood loss was". The assessment may then quantify the patient response as a blood loss that was: i) light, ii) moderate, iii) heavy, or iv) very heavy. Alternatively, the measure may be quantified in terms of a scale of from one to four where one represents light, two represents moderate, three represents heavy and four represents very heavy.

The assessment of a patient's limitation due to the blood loss may include and evaluation of the patient's blood loss limitation on physical activities and/or how much the patient's blood loss limited their social and leisure activities. Assessment of the limitations on work, physical, social and leisure activities may be quantitated as: i) not at all, ii) slightly, iii) moderately, iv) quite a bit, or v) extremely. Alternatively the measure may be quantified in terms of a scale of from one to five where one represents not at all, two represents slightly, three represents moderately, four represents quite a bit, and five represents extremely.

Activities limited may include, but are not limited to, walking, standing, climbing stairs, squatting or bending down, playing with children and attending school activities. Home management activities include, but are not limited to, cooking, cleaning, yard work, and laundry. Leisure activities may include, but are not limited to, dancing, dinner, and movies. Sports activities may include, but are not limited to, tennis, golf, running, swimming, hiking, biking, boating, baseball, softball, basketball, soccer, fencing, volleyball, and other sports related activities.

Once the initial patient assessment measures have been completed and the patient has been identified as in need of treatment, the patient is administered a therapeutically effective treatment regimen of an antifibrinolytic agent. Suitable antifibrinolytic agents contemplated for use in the present invention include, but are not limited to tranexamic acid, aminocaproic acid, pharmaceutically acceptable salts, esters, derivatives, pro-drugs, metabolites, and analogues of any of the foregoing antifibrinolytic agents.

In certain embodiments the preferred antifibrinolytic agent is tranexamic acid. The tranexamic acid utilized in the present invention can be formulated into any suitable dosage form. Preferably, the tranexamic acid is in the form of a release modified tranexamic acid formulation.

When the preferred antifibrinolytic is tranexamic acid, the therapeutically effective treatment regimen contemplated by the present invention includes administration of a single dose of a tranexamic acid ranging from about 650 mg to about 1300 mg three (3) times a day for at least one day of menstruation, but not more than five days (or 15 single doses). The treatment regimen may be administered for at least one day; for at least the first two days, for at least the first three days, for days two through three, for days two to three, for the duration of menstruation.

In certain embodiments the tranexamic acid treatment regimen for treating the heavy menstrual bleeding includes administration of a single dose of about 650 mg to about 1.3 gm of a modified release formulation three (3) times a day, wherein the modified release formulation contains the tranexamic acid in combination with a modified release material

In certain other embodiments, the present invention is directed to a method of evaluating the effectiveness of a treatment regimen administered for heavy menstrual bleeding.

Evaluation of the effectiveness of the treatment regimen can be initiated at the end of the patient's menstrual period, but prior to completion of the menstrual cycle. The post-menstruation measures provide in part the pharmacology (or therapy assessment) measure described above.

The pharmacology assessment may begin with one or more of the same series of measures utilized during the initial patient assessment, which include: a) determining a patient's perceived blood loss volume during their most recent menstrual period; b) determining how much the patient's blood loss limited their work outside and inside the home; c) determining how much the patient's blood loss limited their physical activities; d) determining how much the patient's blood loss limited their social and leisure activities; e) determining the specific activities that were limited by the patient's blood loss.

Alternatively, an evaluation of the effectiveness of the treatment regimen may require determining the change in the patient's perceived blood loss during the most recent men-

strual period in comparison to the blood loss during the patient's previous menstrual period, measure 1 of FIG. 7 and/or an assessment of the improvement achieved, measure 6 of FIG. 7.

For example, a change in the patients perceived blood loss of about one unit for example from "heavy" to "moderate" or from a score of 3 ("heavy") to a score of 2 ("moderate") would provide the basis for continued treatment. While a perceived loss of less than one unit would suggest either a discontinuation of treatment or a second course after which the evaluation would be reconsidered. Alternatively, or in addition to the blood loss assessment, the practitioner may rely on the assessment in which the comparison of perceived loss is assessed as: i) "about the same", ii) "better", and iii) "worse", as prescribed in measure 6 in FIG. 1. When a patient's response is "about the same", an alternative treatment regimen may be considered for the next menstrual period. The practitioner may also reconsider re-administering the same treatment regimen for an additional menstrual period and later re-evaluate. When a patient's response is "better", the assessment may continue by requiring the patient to provide further information about the improvement in menstrual bleeding. For example, the assessment may include "if your menstrual bleeding improved since your last period, please indicate how much" (measure 6b of the MI of FIG. 7). Answers to this inquiry about an improvement in menstrual bleeding may require the patient to provide an answer such as: i) a very great deal better; ii) a great deal better; iii) a good deal better; iv) an average amount better; v) somewhat better; vi) a little better; or vii) almost the same, hardly better at all. Alternatively the answers can be scaled on a seven unit scale where "a very great deal better" is assigned a value of 7 and "almost the same" is valued as 7.

When a patient's response to measure 6 is "worse", the inquiry continues by requiring the patient to provide further data characterizing the change in menstrual bleeding. For example, the inquiry may determine "if your menstrual period worsened since your last period, please indicate how much" (measure 6c of MI of FIG. 7). Data for this measure to a worsening in menstrual bleeding may require the patient to provide a ranking such as: i) "a very great deal worse"; ii) "a great deal worse"; iii) "a good deal worse"; iv) "an average amount worse"; v) "somewhat worse"; vi) "a little worse"; or vii) "almost the same, hardly worse at all". As before the answers may be scaled on a seven unit scale where −1 is "almost the same" and −7 is "a very great deal worse".

The comparison of perceived blood loss which results in an improvement of at least one unit as measured by measure 1 of FIG. 7 and/or an assessment of a perceived blood loss which is "better" as provided in measure six of FIG. 1 may proceed by assessing whether the improvement "was a meaningful or an important change" to the patient (measure 6c of MI of FIG. 7).

The information obtained about the "improvement" or "worsening" in menstrual bleeding allows the practitioner to make an evaluation of the effectiveness of the treatment regimen which correlates with the change in blood loss as measured by the alkaline hematin test and demonstrated with clinical trial data.

The method for evaluating the effectiveness of a treatment regimen of the present invention may be repeated after each menstrual period. The data obtained from the initial patient assessment and the subsequent pharmacology (therapy assessment) can be stored into a computer database and utilized for future diagnostic and/or evaluation purposes.

In certain other embodiments, the present invention is directed to a method of treating heavy menstrual bleeding. The method involving, evaluating symtomatic data gathered from the measures individually or collectively as described in FIG. 1. (items one through four and six as discussed above) to determine the need for therapy and then administering, to a patient in need, a therapeutically effective treatment regimen of an antifibrinolytic agent, e.g., a release modified tranexamic acid formulation, wherein the treatment regimen is to be administered for part or for the duration of menstruation, but no longer than 5 days during the patient's menstrual cycle.

The present invention is further described with regard to the following examples.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention will be further appreciated with respect to the following non-limiting examples. Other variations or embodiments of the invention will also be apparent to one of ordinary skill in the art from the above descriptions and examples. Thus, the forgoing embodiments are not to be construed as limiting the scope of this invention.

Example 1

Modified release 650 mg tranexamic acid tablets were prepared having the ingredients listed in the Table 1 below:

TABLE 1

Ingredient	Quantity per batch (kg)	Quantity per tablet (mg)
Active Ingredient		
Tranexamic Acid, EP	84.50	650.0
Inactive Ingredients		
Microcrystalline Cellulose NF (Avicel PH 101)	5.753	44.25
Colloidal Silicon Dioxide NF	0.0975	0.75
Pregelatinized Corn Starch, NF	6.435	49.50
Hypromellose, USP (Methocel K3 Premium LV)	19.110	147.00
Povidone, USP (K value range 29-32)	4.680	36.00
Stearic Acid, NF (powder)	2.340	18.00
Magnesium Stearate, NF (powder)	0.585	4.50
Purified Water USP*	17.550	135.00

*Purified water is removed during processing

The formulation of Example 1 was prepared as follows:

1. Weigh all ingredients and keep in moisture resistant containers until ready for use.
2. Measure water into a container. Mix povidone at medium speed until completely dissolved.
3. Add tranexamic acid, microcrystalline cellulose (MCC), pregelatinized corn starch, and colloidal silicon dioxide to the high shear mixer.
4. Mix using impeller only.
5. Mix for an additional time (impeller only). Add all of the povidone solution during this mixing step.
6. Mix until adequately granulated (impeller and chopper). Proceed only when desired granulation has been achieved. Add additional water if necessary.
7. Dry the granulation to moisture content of NMT 1.2%.
8. Pass the granulation through the oscillating granulator equipped with a #30 mesh screen. Weigh the granulation. Add granulation to the V-Blender.
9. Add the hypromellose USP Methocel K3 Premium to the V-blender. Blend.
10. Pass magnesium stearate and stearic acid through oscillating granulator equipped with a #40 mesh screen. Add magnesium stearate and stearic acid to the V-blender and blend.

11. Perform specified physical property testing. Proceed to compression.
12: Compress tablets to desired weight.

Example 2

In Example 2, immediate release 650 mg tranexamic acid tablets were prepared having the ingredients listed in Table 2 below:

TABLE 2

Ingredient	Quantity per batch (kg)	Quantity per tablet (mg)
Active Ingredient		
Tranexamic Acid, EP (650 mg/tab)	84.50	650.0
Inactive Ingredients		
Microcrystalline Cellulose, NF (Avicel PH 101)	5.753	44.25
Microcrystalline Cellulose, NF (Avicel PH 102)	10.660	82.00
Colloidal Silicon Dioxide, NF	0.0975	0.75
Pregelatinized Corn Starch, NF	6.435	49.50
Croscarmellose Sodium, NF	19.50	15.00
Povidone, USP (K value range 29-32)	4.680	36.00
Stearic Acid, NF (powder)	2.340	18.00
Magnesium Stearate, NF (powder)	0.585	4.50
Purified Water, USP*	17.550	135.00
Film Coating (Inactive Ingredients)**		
Opadry White YS-1-7003	4.110	—
Purified Water, USP	36.990	—

*Purified water is removed during processing
**6 kg excess prepared to account for losses during transfer

The formulation of Example 2 was prepared as follows:
1. Weigh all ingredients and keep in moisture resistant containers until ready for use.
2. Measure water into a container. Mix povidone at medium speed until completely dissolved.
3. Add tranexamic acid, microcrystalline cellulose (MCC), pregelatinized corn starch, and colloidal silicon dioxide to the high shear mixer.
4. Mix using impeller only.
5. Mix for an additional time (impeller only). Add all of the povidone solution during this mixing step.
6. Mix until adequately granulated (impeller and chopper). Proceed only when desired granulation has been achieved. Add additional water if necessary.
7. Dry the granulation to moisture content of NMT 1.2%.
8. Pass the granulation through the oscillating granulator equipped with a #30 mesh screen. Weigh the granulation. Add granulation to the V-Blender.
9. Add the croscarmellose sodium and MCC to the V-Blender and blend.
10. Pass magnesium stearate and stearic acid through oscillating granulator equipped with a #40 mesh screen. Add magnesium stearate and stearic acid to the V-blender and blend.
11. Perform specified physical property testing. Proceed to compression.
12. Compress tablets.
12. After compression, spray coat the compressed dosage forms with the Opadry White in water.

Example 3

In Example 3, modified release 650 mg tranexamic acid tablets were prepared as in Example 1 and coated with a film coating similar to the immediate release tablets of Example 2. The ingredients are listed in Table 3 below:

TABLE 3

Ingredient	Quantity per batch (kg)	Quantity per tablet (mg)
Active Ingredient		
Tranexamic Acid, EP	84.50	650.0
Inactive Ingredients		
Microcrystalline Cellulose NF (Avicel PH 101)	5.753	44.25
Colloidal Silicon Dioxide NF	0.0975	0.75
Pregelatinized Corn Starch, NF	6.435	49.50
Hypromellose, USP (Methocel K3 Premium LV)	19.110	147.00
Povidone, USP (K value range 29-32)	4.680	36.00
Stearic Acid, NF (powder)	2.340	18.00
Magnesium Stearate, NF (powder)	0.585	4.50
Purified Water USP*	17.550	135.00
Film Coating (Inactive Ingredients)**		
Opadry White YS-1-7003	4.305	—
Purified Water, USP	38.750	—

*Purified water is removed during processing
**6 kg excess prepared to account for losses during transfer

Example 3a

Example 3A, delayed release 650 mg tranexamic acid tablets were prepared having the ingredients listed in Table 3A below:

TABLE 3A

Ingredient	Quantity per batch (kg)	Quantity per tablet (mg)
Active Ingredient		
Tranexamic Acid, EP	84.50	650.0
Inactive Ingredients		
Microcrystalline Cellulose NF (Avicel PH 101)	5.753	44.25
Microcrystalline Cellulose NF (Avivel PH 102)	10.660	82.00
Colloidal Silicon Dioxide NF	0.0975	0.75
Pregelatinized Corn Starch, NF	6.435	49.50
Croscarmellose Sodium NF	19.50	15.00
Povidone, USP (K value range 29-32)	4.680	36.00
Stearic Acid, NF (powder)	2.340	18.00
Magnesium Stearate, NF (powder)	0.585	4.50
Purified Water USP*	17.550	135.00
Film Coating (Inactive Ingredients)**		
Acryl-Eze (930185359)	12.90	—
Silicone Emulsion, 30%	0.323	—
Purified Water, USP	51.271	—

*Purified water is removed during processing; mg per tablet is based on theoretical specific gravity of 1.0 g/ml
**6 kg excess prepared to account for losses during transfer

The formulation of Example 3A was prepared as follows:
1. Weigh all ingredients and keep in moisture resistant containers until ready for use.
2. Measure water into a container. Mix povidone at medium speed until completely dissolved.
3. Add tranexamic acid, microcrystalline cellulose (MCC), pregelatinized corn starch, and colloidal silicon dioxide to the high shear mixer.
4. Mix using impeller only.
5. Mix for an additional time (impeller only). Add all of the povidone solution during this mixing step.

6. Mix until adequately granulated (impeller and chopper). Proceed only when desired granulation has been achieved. Add additional water if necessary.
7. Dry the granulation to moisture content of NMT 1.2%.
8. Pass the granulation through the oscillating granulator equipped with a #30 mesh screen. Weigh the granulation. Add granulation to the V-Blender.
9. Add the croscarmellose sodium and MCC to the V-Blender and blend.
10. Pass magnesium stearate and stearic acid through oscillating granulator equipped with a #40 mesh screen. Add magnesium stearate and stearic acid to the V-blender and blend.
11. Perform specified physical property testing. Proceed to compression.
12. Compress tablets.
13. After compression, spray coat the compressed dosage forms with the film coating.

Dissolution results for the delayed release formulation of Example 3A (in base stage) are listed below in Table 3B.

Dissolution Results for the Delayed Release Formulation (in Base Stage)

TABLE 3B

Time (min.)	Dissolution (%)	Standard Deviation
15	16%	±6.013873
30	89%	±14.06769
45	95%	±2.810694
60	97%	±2.345208

Example 4

Bioavailability and Bioequivalence Evaluation

In Example 4, a comparative, randomized, single dose, 4-way Crossover Absolute Bioavailability (BA) and Bioequivalence (BE) study of Tranexamic Acid Tablet Formulations prepared in accordance with Examples 1 and 2 in Healthy Adult Women Volunteers under Fasting Conditions was performed. The objective was to assess the bioequivalence of a 650 mg modified release tablet formulation prepared in accordance with Example 1 compared to the immediate release reference tablet formulation of tranexamic acid prepared in accordance with Example 2, and to determine the bioavailability of the modified tablet formulation to the approved IV (1 g) formulation Cyklokapron® by Pharmacia & Upjohn. The design was a randomized, 4-way crossover, comparative BE and BA determination. All oral doses administered were 1.3 g. Twenty-eight (28) healthy non-smoking adult female volunteer subjects were enrolled in the study. A total of 26 subjects completed the study. Sample size was calculated assuming a 25% CV in AUC_{inf}. The study endpoints were the 90% confidence intervals of the ratio of least-squares means of the pharmacokinetic parameters AUC_{0-t}, AUC_{inf}, and C_{max} of the modified release formulation to the immediate-release formulation from serum concentration-time data drawn up to 36 hours after a single dose of drug. In addition, the bioavailability of the tablet formulations were calculated. Smokers, oral contraceptive users, those with a previous history of thromboembolic events and altered vision were excluded from the study. ECG monitoring was performed before, during and after the estimated times of peak serum tranexamic acid concentrations exposure. Adverse events were captured and recorded throughout the trial period.

In the study, subjects were randomized to receive single oral 1.3 g (2×650 mg tablets) dose of tranexamic acid in tablet forms which included a modified release dosage form and an immediate release dosage form. Subjects were also administered a single 1 g (10 ml) IV solution of tranexamic acid (100 mg/ml concentration).

A summary of the pharmacokinetic results from the study of Example 4 are listed in the tables below.

TABLE 4

Summary of Results - Tranexamic Acid in Plasma Pharmacokinetic Parameters (N = 26)

	ln AUC 0-t* (mcg · h/mL)	ln AUCinf* (mcg · h/mL)	ln Cmax* (mcg/mL)
Modified Release formulation			
Mean	66.703	69.642	11.251088
CV	26.8	27.2	29.1
N	26	24	26
Immediate Release formulation			
Mean	70.157	72.656	12.260414
CV	16.2	16.4	23.0
N	26	24	26
Least-Squares Mean:			
Modified Release	66.935	68.891	11.321919
Immediate Release	70.051	72.411	12.258222
Ratio of Least-Squares Mean (modified release/immediate release) %	95.6	95.1	92.4

*For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
AUCinf, kel, half-life and F could not be estimated for some subjects.
AUC 0-t is the area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.

TABLE 5

Summary of Results - Tranexamic Acid in Plasma Pharmacokinetic Parameters (N = 26)

	Tmax (h)	Half-life (h)	kel (1/h)	F (%)
Modified Release formulation				
Mean	2.942	11.370	0.06300	44.93
CV	22.7	17.6	19.4	25.3
n	26	26	26	24
Immediate Release formulation				
Mean	2.808	11.013	0.06438	46.04
CV	20.8	15.5	15.3	16.1
n	26	24	24	24

TABLE 6

Summary of Results - Tranexamic Acid in Plasma Pharmacokinetic Parameters (N = 26)

	Ln AUC 0-t* (mcg · h/mL)	ln AUCinf* (mcg · h/mL)	ln Cmax* (mcg/mL)
90% Confidence Intervals (Modified release/Immediate release) %			
lower limit:	87.8%	87.4%	84.0%
upper limit:	104.0%	103.5%	101.6%
p-Value (ANOVA)			
Modified vs Immediate	0.3721	0.3259	0.1676
Period	0.0704	0.0499	0.0356
Sequence	0.7734	0.7978	0.8207
Intrasubject CV %	18.3	17.4	20.6

*For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
AUCinf, kel, half-life and F could not be estimated for some subjects.

Concentration-time profiles for the study of Example 4 are presented on semi-log and linear scale over 36 hours and are depicted in FIGS. **3** and **4**.

The following pharmacokinetic parameters in the table below were calculated for tranexamic acid in plasma for the study of Example 4.

MRT: The mean residence time (MRT) after intravenous administration of tranexamic acid was determined using the equation,

AUMC/AUC+infusion time/2,

where the AUMC is the area under the moment-time curve.

MTT: Following oral administration of the Modified Release and Immediate Release formulations, the mean transit time (MTT) of tranexamic acid was calculated by dividing the AUMC by the AUC.

MAT: The mean absorption time (MAT) for the two formulations was derived by subtracting the MRT from the MTT.

Mean (±SD) results are presented in the table below:

TABLE 7

	IV	Modified Release	Immediate Release
MRT (hours)	3.51 ± 0.38	N/A	N/A
MTT (hours)	N/A	7.70 ± 0.72	7.21 ± 1.01
MAT (hours)	N/A	4.18 ± 0.70	3.70 ± 0.94

The mean transit time (MTT) and mean absorption time (MAT) of the Modified Release formulation of tranexamic acid was approximately 30 minutes longer than that observed for the Immediate Release formulation.

The most frequently reported adverse events from the study of Example 4 are listed in the table below. The table lists the number of subjects reporting adverse events, and the percentage of subjects is in parentheses.

TABLE 8

	Treatment		
Adverse Events	Modified Release (2 × 650 mg) (n = 27)	Immediate Release (2 × 650 mg) (n = 27)	IV solution (10 × 100 mg/ml) (n = 27)
Headache	4 (15%)	7 (26%)	7 (26%)
Nausea	0 (0%)	2 (7%)	10 (37%)
Dizziness	0 (0%)	0 (0%)	11 (41%)
Feeling Hot	0 (0%)	0 (0%)	6 (22%)
Nasal Congestion	2 (7%)	1 (4%)	1 (4%)
Cough	0 (0%)	0 (0%)	2 (7%)
Urine odor abnormal	2 (7%)	0 (0%)	1 (4%)

Dissolution Results for Immediate Release and Modified Release Formulations prepared in accordance with Examples 2 and 1 respectively used in the study of Example 4 tested under USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. are listed in the tables below.

TABLE 9

Dissolution Results for the Immediate Release Formulation in Table 2.

Time (min.)	Dissolution (%)	Standard Deviation
15	58.0%	±9.521905
30	96.0%	±10.2697
45	102.0%	±0.408248
60	104.0%	±1.032796

TABLE 10

Dissolution Results for the Modified Release Formulation in Table 1

Time (min.)	Dissolution (%)	Standard Deviation
15	21.0%	±1.414214
30	40.0%	±2.810694
45	58.0%	±3.600926
60	73.0%	±3.81663
90	98.0%	±2.097618

TABLE 10A

Dissolution Results for the Various Batches of the Modified Release Formulation Table 1

Batch #	0 min	15 min	45 min	90 min	Standard Deviation			
Batch 1	0	21	58	98	0	±1.386	±3.48	±2.254
Batch 2	0	21	58	95	0	±1.134	±3.074	±2.47
Batch 3	0	23	59	93	0	±2.323	±4.366	±3.627
Batch 4	0	21	56	89	0	±1.575	±3.808	±2.492
Batch 5	0	24	59	93	0	±2.016	±3.422	±2.139
Batch 6	0	25	67	100	0	±1.45	±3.149	±0.9
Batch 7	0	22	58	94	0	±0.968	±2.32	±2.068
Batch 8	0	29	69	98	0	±2.03	±3.726	±1.666
Batch 9	0	28	66	96	0	±2.268	±3.762	±2.688
Batch 10	0	15	65	93	0	±1.904	±2.47	±2.604
Batch 11	0	27	64	92	0	±1.836	±2.368	±2.024

CONCLUSIONS

The ratios of least-squares means and the 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC_{0-t}, AUC_{inf} and C_{max} for

tranexamic acid in plasma were within the 80-125% Food and Drug Administration (FDA) acceptance range for the modified release formulation versus the immediate release formulation under fasting conditions.

The absolute bioavailability of the modified release and immediate release tablet formulations were 44.93% and 46.04% respectively.

Based on these results, the modified release tranexamic acid tablet formulation and the immediate release tranexamic acid formulation are bioequivalent under fasting conditions.

Example 4a

Comparative Example

In Comparative Example 4A, a 500 mg immediate release tranexamic acid tablet, approved and marketed in Canada under the name Cyklokapron was obtained and dissolution tested under USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. The dissolution results are listed in Table 10A below:

TABLE 10A

Sample #	% dissolved in 15 min.	% dissolved in 30 min.	% dissolve in 45 min.	% dissolved in 60 min.
1	102	104	105	106
2	102	104	105	106
3	101	102	102	105
4	99	101	102	103
5	100	102	103	104
6	99	101	102	104
Average	101	102	103	105
% RSD	1.4	1.3	1.4	1.1

Example 5

In Example 5, based on single dose pharmacokinetic parameters, pharmacokinetic simulations of serum concentrations were performed to compare dosing the modified release formulation of Example 4 at every 8 hours (Q8H: at 6:00 AM, 2:00 PM, 10:00 PM) and dosing three times a day, other than every 8 hours (TID: at 8:00 AM, 2:00 PM, and 10:00 PM). The results are provided in Tables 11-14 below.

TABLE 11

Tranexamic Acid - Modified Release Formulation
Dosage Regimen Simulation - ORAL
1.3 g q8 hr

Time (h)	Dose (mcg)	Conc. (mcg/mL)
0	1.30E+06	0
1	0	4.0594
2	0	10.0551
3	0	10.6433
4	0	9.20306
5	0	7.26932
6	0	5.4699
8	1.30E+06	2.89909
9	0	6.15391
10	0	11.5813
11	0	11.7752
12	0	10.0646
13	0	7.94622
14	0	6.02067
15	0	4.4712
16	1.30E+06	3.30248
17	0	6.51406
18	0	11.9097

TABLE 11-continued

Tranexamic Acid - Modified Release Formulation
Dosage Regimen Simulation - ORAL
1.3 g q8 hr

Time (h)	Dose (mcg)	Conc. (mcg/mL)
19	0	12.0794
20	0	10.3495
21	0	8.21523
22	0	6.2761
23	0	4.71463
24	1.30E+06	3.53505
25	0	6.73663
26	0	12.1229
27	0	12.2838
28	0	10.5455
29	0	8.40336
30	0	6.45664
31	0	4.88791
32	1.30E+06	3.70138
33	0	6.89628
34	0	12.2762
35	0	12.4309
36	0	10.6868
37	0	8.53894
38	0	6.5868
39	0	5.01286
40	1.30E+06	3.82133
41	0	7.01144
42	0	12.3867
43	0	12.537
44	0	10.7887
45	0	8.63675
46	0	6.68069
47	0	5.103
48	1.30E+06	3.90786
49	0	7.09451
50	0	12.4665
51	0	12.6136
52	0	10.8621
53	0	8.70731
54	0	6.74842
55	0	5.16802
56	1.30E+06	3.97028
57	0	7.15443
58	0	12.524
59	0	12.6688
60	0	10.9152
61	0	8.7582
62	0	6.79728
63	0	5.21493
64	1.30E+06	4.01531
65	0	7.19766
66	0	12.5655
67	0	12.7087
68	0	10.9534
69	0	8.79492
70	0	6.83253
71	0	5.24877
72	1.30E+06	4.0478
73	0	7.22885
74	0	12.5954
75	0	12.7374
76	0	10.981
77	0	8.82141
78	0	6.85796
79	0	5.27318
80	1.30E+06	4.07124
81	0	7.25135
82	0	12.617
83	0	12.7581
84	0	11.0009
85	0	8.84052
86	0	6.87631
87	0	5.29079
88	1.30E+06	4.08814
89	0	7.26758
90	0	12.6326
91	0	12.7731
92	0	11.0153

TABLE 11-continued

Tranexamic Acid - Modified Release Formulation Dosage Regimen Simulation - ORAL 1.3 g q8 hr		
Time (h)	Dose (mcg)	Conc. (mcg/mL)
93	0	8.8543
94	0	6.88954
95	0	5.3035
96	1.30E+06	4.10034
97	0	7.27929
98	0	12.6439
99	0	12.7839
100	0	11.0256
101	0	8.86425
102	0	6.89909
103	0	5.31266
104	1.30E+06	4.10913
105	0	7.28773
106	0	12.652
107	0	12.7917
108	0	11.0331
109	0	8.87142
110	0	6.90597
111	0	5.31927
112	1.30E+06	4.11548
113	0	7.29382
114	0	12.6578
115	0	12.7973
116	0	11.0385
117	0	8.8766
118	0	6.91094
119	0	5.32404
120	0	4.12006

Concentration-time profiles are presented over 120 hours for the modified release formulation in Table 12 and are depicted in FIG. 1. A 1 g formulation administered q8h is also depicted for comparison purposes.

TABLE 12

Cmax, Cmin and Cavg for 1.3 g q8 hr simulation Simulation at 120 hours	
Pharmacokinetic Parameter	Concentration
Cmax	12.8 mcg/mL
Cmin	4.1 mcg/mL
Cavg	8.4 mcg/ml

TABLE 13

Tranexamic Acid - Modified Release Formulation Dosage Regimen Simulation - ORAL 1.3 g TID (8:00 AM, 2:00 PM, and 10:00 PM)		
Time (h)	Dose (mcg)	Conc. (mcg/mL)
0	1.30E+06	0
1	0	4.0594
2	0	10.0551
3	0	10.6433
4	0	9.20306
5	0	7.26932
6	1.30E+06	5.4699
8	0	12.9542
9	0	12.7378
10	0	10.7293
11	0	8.40129
12	1.30E+06	6.33141
13	0	8.74352
14	0	13.505
15	0	13.2018

TABLE 13-continued

Tranexamic Acid - Modified Release Formulation Dosage Regimen Simulation - ORAL 1.3 g TID (8:00 AM, 2:00 PM, and 10:00 PM)		
Time (h)	Dose (mcg)	Conc. (mcg/mL)
16	0	11.1327
17	0	8.76144
18	0	6.65976
19	0	4.98823
20	0	3.73474
21	0	2.8275
22	0	2.18502
23	0	1.73555
24	1.30E+06	1.42243
25	0	5.26298
26	0	11.104
27	0	11.5807
28	0	10.058
29	0	8.06103
30	1.30E+06	6.21137
31	0	8.76659
32	0	13.6187
33	0	13.3709
34	0	11.334
35	0	8.97998
36	1.30E+06	6.88576
37	0	9.27495
38	0	14.0147
39	0	13.6908
40	0	11.6019
41	0	9.21185
42	0	7.09208
43	0	5.40321
44	0	4.1331
45	0	3.20991
46	0	2.55212
47	0	2.08796
48	1.30E+06	1.76074
49	0	5.58776
50	0	11.4158
51	0	11.88
52	0	10.3453
53	0	8.33688
54	1.30E+06	6.47618
55	0	9.02081
56	0	13.8627
57	0	13.6052
58	0	11.5589
59	0	9.1959
60	1.30E+06	7.09304
61	0	9.47395
62	0	14.2057
63	0	13.8742
64	0	11.778
65	0	9.38036
66	0	7.25433
67	0	5.55898
68	0	4.28264
69	0	3.35346
70	0	2.68993
71	0	2.22026
72	1.30E+06	1.88775
73	0	5.70968
74	0	11.5329
75	0	11.9924
76	0	10.4532
77	0	8.44044
78	1.30E+06	6.57559
79	0	9.11625
80	0	13.9543
81	0	13.6931
82	0	11.6434
83	0	9.27696
84	1.30E+06	7.17086
85	0	9.54865
86	0	14.2775
87	0	13.943
88	0	11.8441
89	0	9.44431

TABLE 13-continued

Tranexamic Acid - Modified Release Formulation
Dosage Regimen Simulation - ORAL
1.3 g TID (8:00 AM, 2:00 PM, and 10:00 PM)

Time (h)	Dose (mcg)	Conc. (mcg/mL)
90	0	7.31525
91	0	5.61745
92	0	4.33877
93	0	3.40735
94	0	2.74167
95	0	2.26992
96	1.30E+06	1.93543
97	0	5.75546
98	0	11.5768
99	0	12.0346
100	0	10.4937
101	0	8.47931
102	1.30E+06	6.61292
103	0	9.15208
104	0	13.9887
105	0	13.7261
106	0	11.6751
107	0	9.30739
108	1.30E+06	7.20008
109	0	9.5767
110	0	14.3044
111	0	13.9689
112	0	11.8689
113	0	9.46813
114	0	7.33811
115	0	5.63941
116	0	4.35985
117	0	3.42759
118	0	2.76109
119	0	2.28857
120	0	1.95333

Concentration-time profiles are presented over 120 hours for the modified release formulation in Table 14 and are depicted in FIG. 2. A 1 g formulation administered TID is also depicted for comparison purposes.

TABLE 14

Cmax, Cmin and Cavg for 1.3 g TID
(8:00 AM, 2:00 PM, and 10:00 PM)
Simulation at 120 hours

Pharmacokinetic Parameter	Conc.
Cmax	12.0, 14.0, 14.3 mcg/mL
Cmin	1.9, 6.6, 7.2 mcg/mL
Cavg	8.4 mcg/mL

Example 6

In Example 6, a study of a single dose followed by multiple doses, was performed on 20 healthy non-smoking adult female volunteers using a modified release formulation prepared in accordance with Example 1. After an overnight fast, subjects received a single oral dose of tranexamic acid (1.3 g) on Day 1. Blood samples were taken before dosing and up to 36 hours post-dose. Subjects received another single oral dose of tranexamic acid (1.3 g) on the evening of Day 2, and 3 times a day (every 8 hours) starting on the morning of Day 3 until the last dose on the morning of Day 7. Blood samples were taken before the 6th, 9th, 12th and 15th dose (the last dose) for the determination of C_{min}, and up to 8 hours after the last dose, for the determination of drug concentration at steady-state. Subjects were housed from at least 10 hours before the 1st dose on Day 1 until after the 8-hour blood draw following the 15th dose (on Day 7).

Tranexamic acid is minimally bound (approximately 3%) to plasma proteins (mainly plasminogen) at "typical" therapeutic plasma concentrations of approximately 5-15 mg/L. The main route of elimination of tranexamic acid is renal glomerular filtration. After oral administration of tranexamic acid (250 or 500 mg) to healthy adults, between 40-70% of the administered dose is excreted unchanged in the urine within 24 hours. After IV administration (1 g) 30% of the dose is excreted unchanged in the urine within one hour, 45-55% within 2-3 hours and 90% within 24 hours.

The beta elimination half-life of tranexamic acid is 2 hours. Based on published data, the mean C_{max} and AUC_{0-6} pharmacokinetic parameters after a single 1.3 g oral dose of tranexamic acid are expected to be approximately 65% of those achieved with a 2 g dose (i.e. ~10 mg/L and ~40 mg-h/L, C_{max} and AUC_{0-6} under fasting conditions, respectively).

However, the pharmacokinetics of tranexamic acid were not adequately characterized in Pilbrant, et al., *Eur. J. Clin. Pharmacol*, (1981)-20:65-72, since blood samples were collected for up to only 6 hours post-dose. In addition, the plasma concentration-time curves after IV administration showed three exponential phases, with a gamma elimination half-life of approximately 7 hours. For this reason, the concentration-time profile of tranexamic acid was estimated by simulating the data over 36 hours, after oral administration of a 1.3 g dose under fasting conditions, using NONMEM. Based on the simulation results, it would be appropriate to collect blood samples until 36 hours in order to characterize the AUC, Cmax, tmax, t½ and F.

The objective of this study of Example 6 was to assess the pharmacokinetic linearity of the test tablet formulation of tranexamic acid (modified release), after a single oral dose (Day 1) compared to a daily (1.3 g every 8 hours) dosage regimen (Days 2 to 7), under fasting conditions.

In the study of Example 6, blood samples (1×5 mL) were collected in blood collection tubes containing lithium heparin at Hour 0 (pre-dose) on Day 1, and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 14, 24, 28, 32, and 36 hours post-dose. Blood samples for Cmin determinations were also collected immediately before the 6th, 9th, 12th, and 15th doses on Days 4, 5, 6, and 7, respectively, and at the following times after the 15th dose: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, and 8 hours. Plasma samples were separated by centrifugation, then frozen at −20° C.±10° C. and kept frozen until assayed at AAI Development Services in New-Ulm, Germany.

Noncompartmental Pharmacokinetic Parameters

Calculations for plasma tranexamic acid were calculated by noncompartmental methods using the following pharmacokinetic parameters in Tables 15 and 16:

Day 1:

TABLE 15

AUC 0-t:	The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.
AUCinf:	The area under the plasma concentration versus time curve from time 0 to infinity. AUCinf was calculated as the sum of AUC 0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.
AUC/AUCinf:	The ratio of AUC 0-t to AUCinf.
Cmax:	Maximum measured plasma concentration over the time span specified.
tmax:	Time of the maximum measured plasma concentration. If the maximum value occured at more than one time point, tmax was defined as the first time point with this value.

TABLE 15-continued

kel:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. This parameter was calculated by linear least squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g. three or more non-zero plasma concentrations).
t½:	The apparent first-order terminal elimination half-life was calculated as 0.693/kel.

No value for kel, AUCinf or t½ were reported for cases that did not exhibit a terminal log-linear phase in the concentration versus time profile.

Day 7:

TABLE 16

AUCτ:	The area under the plasma concentration versus time curve over the final dosing interval, as calculated by the linear trapezoidal method.
Cmax:	Maximum measured plasma concentration over the final dosing interval.
Cmin:	Measured plasma concentration prior to the morning dose.
tmax:	Time of the maximum measured plasma concentration over the final dosing interval. If the maximum value occurred at more than one time point, tmax was defined as the first time point with this value.
Flux:	Percent fluctuation was calculated as follows: Flux 1: $\frac{Cmax - Cmin}{Cssav} \times 100$ where Cssav was calculated as the ratio of AUC 0-τ to the dosing interval, τ. Flux 2: $\frac{Cmax - Cmin}{Cmin} \times 100$

Compartmental Pharmacokinetic Parameters

Compartmental analysis was performed on tranexamic acid data following single and multiple oral administrations of the modified release (MR) tablet formulation. Multiple compartmental models were constructed and their ability to fit plasma concentrations of tranexamic acid were evaluated using a standard two-stage (STS) approach with ADAPT-II (maximum likelihood analysis). The discrimination process was performed by computing the Akaike Information Criterion Test (AIC), the minimum value of the objective function (OBJ) and by looking at pertinent graphical representations of goodness of fit (e.g. fitted and observed concentrations versus time).

The final analysis was performed using an iterative two-stage approach with the IT2S® software. This software uses a population methodology which allows one to provide robust PK parameter estimates on an individual subject and population basis. All relevant pharmacokinetic parameters were calculated and reported. Concentrations were modeled using a weighting procedure of $W_j=1/S_j^2$ where the variance σj^2 was calculated for each observation using the equation $\sigma j^2=(a+b*Y_j)^2$ where a and b are the intercept and slope of each variance model. The slope is the residual variability associated with each concentration (includes the intra-individual variability and the sum of all experimental errors), and the intercept is related to the limit of detection of the analytical assay. All PK parameter estimates were updated iteratively during the population PK analysis (VARUP, IT2S®) until stable values were found. The analysis included the quantitative estimation of population PK parameters and interindividual variability of tranexamic acid in plasma.

Individual profiles of observed vs fitted plasma concentrations of tranexamic acid were provided for the MR formulation.

Statistical Analyses

Descriptive Statistics

Descriptive statistics including arithmetic means, standard deviations and coefficients of variation were calculated on the individual concentration and pharmacokinetic data. Additionally, geometric means were calculated for the parameters $AUC_{0-\tau}$, AUC_{inf}, and C_{max} for Day 1 and AUCτ, C_{max} and C_{min} for Day 7.

Time Dependence Pharmacokinetic Linearity

The pharmacokinetic parameter AUCτ (Day 7) was compared against AUC_{inf} (Day 1) using an analysis of variance (ANOVA) on the ln-transformed values for tranexamic acid. The ANOVA model included Group, Day (1 (AUC_{inf}) and 7 (AUCτ)) and the interaction Day*Group as fixed effects. All the interaction terms were not statistically significant, at a level of 5%, and were dropped from the final model. The ANOVA included calculation of least-squares means (LSM), the difference between Day LSM and the standard error associated with this difference. The above statistical analysis was done using the SAS® GLM procedure.

The ratio of LSM was calculated using the exponentiation of the Day LSM from the analysis on the ln-transformed response. The ratio was expressed as a percentage relative to AUC_{inf} (Day 1).

A ninety percent confidence interval for the ratio was derived by exponentiation of the confidence interval obtained for the difference between Day LSM resulting from the analysis on the ln-transformed response. The confidence interval was expressed as a percentage relative to AUC_{inf} (Day 1).

Steady-State Analysis

A steady-state analysis was performed, on the ln-transformed pre-dose Cmin concentrations at −72, −48, −24 and 0-hour time points, using Helmert's contrasts. The ANOVA model included Group, Time and the interaction Time*Group as fixed effects. In order to model the correlations within every subject, an appropriate variance-covariance matrix was chosen among the following: unstructured (UN), compound symmetry (CS), compound symmetry heterogeneous (CSH), variance component (VC), autoregressive (AR(1)), autoregressive heterogeneous (ARH(1)) and autoregressive moving average (ARMA(1,1)), using the Akaike's Burnham and Anderson criterion (AICC). All the interaction terms were not statistically significant, at a level of 5%, and were dropped from the final model. The ANOVA included also calculation of least-squares means (LSM) for each pre-dose C_{min} concentrations. Helmert's contrasts were constructed such that each time point is compared to the mean of subsequent time points. There are 3 contrasts associated to the 4 pre-dose concentration timepoints. They are listed in Table 17 below:

TABLE 17

Contrast	Tests
Compar. 1	Predose Day 4 compared to (mean predose of Day 5, 6 and 7)
Compar. 2	Predose Day 5 compared to (mean predose of Day 6 and 7)
Compar. 3	Predose Day 6 compared to predose Day 7 (0-hour)

The above statistical analyses were done using the SAS® Mixed procedure.

Formula

The following formulae in Table 18 were used for the ratio of least-squares means and 90% confidence interval calculations derived from the ANOVA on the ln transformed pharmacokinetic parameters.

TABLE 18

Ratio of Least-squares Means:	$100 \times e^{(LSM_{Day7}-LSM_{Day1})}$
90% Confidence Interval:	$100 \times e^{(LSM_{Day7}-LSM_{Day1} \pm t_{df,0.05} \times SE_{Day7-Day1})}$

Note:
LSM_{Day7} and LSM_{Day1} are the least-squares means of Day 7 and Day 1, as computed by the LSMEANS statement of the SAS ® GLM procedure.
$t_{df,\alpha}$ is the value of the Student's t distribution with df degrees of freedom (i.e. degrees of freedom for the error term from the analysis of variance) and a right-tail fractional area of α ($\alpha = 0.05$).
$SE_{Day7-Day1}$ is the standard error of the difference between the adjusted Day means, as computed by the ESTIMATE statement in the SAS ® GLM procedure.

Discussion of Pharmacokinetic Results

Time Dependence Pharmacokinetic Linearity

The ANOVA model included Group, Day (1 (AUC_{inf}) and 7 ($AUC\tau$)) and the interaction Day*Group as the fixed effect. All the interaction terms were not statistically significant, at a level of 5%, and were dropped from the final model. Pharmacokinetic linearity was calculated for the formulation using the same approach as above, but the ANOVA model included Group, Day 1 (AUCinf) and Day 7 ($AUC\tau$)) and the interactions Group*Day as fixed effects and Subject nested within Group as a random effect.

The pharmacokinetic linearity results are summarized in the table below.

TABLE 19

		90% Confidence Interval	
Formulation	Ratio AUCτ/AUCinf	Lower Limit	Upper Limit
MR	97.3	86.5	109.5

The pharmacokinetic linearity results indicate that the ratios of least-squares means of $AUC\tau$ (Day 7) to AUC_{inf} (Day 1) and the 90% confidence interval for the MR formulation were within the 80-125% acceptance range. Based on these results, the 650 mg tranexamic acid modified release tablets exhibited linear pharmacokinetics following repeated administration (7 days) of a 1.3 g dose under fasting conditions.

Steady-State Analysis

For the steady-state analysis, the CS variance-covariance matrix was chosen to model the correlations within every subject. Overall, the interaction term (i.e. Time*Group) was not statistically significant and was removed from the final ANOVA model. For each formulation, the same approach as above was used, but the ANOVA models included Group, Time and the interactions Time*Group as fixed effects.

A summary of LSM results for the steady-state analysis are summarized in Table 20A below.

TABLE 20A

Formulation	Days	Times (hour)	LSM derived from the ANOVA
MR	4	−72	4.90536
	5	−48	4.77323
	6	−24	5.23678
	7	0	5.15389

Summary of statistical comparisons for the steady-state analysis are summarized in Table 20B below

TABLE 20B

Formulation	Helmert's contrasts	P-value
MR	Predose Day 4 compared to (mean predose of Day 5, 6 and 7)	0.4438
	Predose Day 5 compared to (mean predose of Day 6 and 7)	0.0393
	Predose Day 6 compared to predose Day 7	0.7318

Based on the results above, steady-state plasma concentration of tranexamic acid were reached on Day 4 (−72-hour), since the p value for the first contrast was not statistically significant at a 5% alpha error. It should be noted that the second comparison [Predose Day 5 compared to (mean of Day 6 and 7)] was found to be statistically significant.

The largest difference observed in predose plasma concentrations of tranexamic acid between the LSM of predose Day 5 compared to Day 6 and 7 was less than 10%, which is not considered clinically relevant. Moreover, the last contrast was not statistically significant and the observed difference between the LSM of predose Day 6 and 7 was less than 2%.

Compartmental Pharmacokinetic Analysis

The mean apparent oral clearance (CL/F) of the MR formulation calculated with compartmental methods was 17.7 L/h (295 mL/min). Based on previous data reported in the literature, the group of Pilbrant, et al., have determined that the urinary recovery of tranexamic acid exceeded 95% of the dose administered. Considering the bioavailability of the MR formulation (Mean F: 44.9%, See Table 5), the systemic clearance (CL) of tranexamic acid (295 mL/min×0.449=123 mL/min) would be close to the glomerular filtration rate in healthy subjects (125 mL/min)5.

Using compartmental methods, the mean T½γ for the MR formulation was 16.6 hours. Similar values of terminal elimination half-life were previously reported in the literature. Pilbrant A., et al., *Eur. J. Clin. Pharmacol* (1981), 20: 65-72.

Following a single oral dose of 1.3 g of the MR formulation, the mean plasma concentrations of tranexamic acid observed at 28, 32, and 36 hours were 0.19724, 0.15672, and 0.13624 mcg/mL, respectively. Considering the therapeutic window of tranexamic acid (5-15 mcg/mL) and the very low plasma concentration levels observed at these timepoints, the terminal elimination half-life (T½γ) characterizing the slow decline of plasma concentrations should not play a clinically significant role in the frequency of drug administration.

Pharmacokinetic Conclusions

The pharmacokinetic linearity results indicate that the ratios of least-squares means of $AUC\tau$ (Day 7) to AUCinf (Day 1) and the 90% confidence interval for the MR formulation were within the 80-125% acceptance range. Based on these results, the 650 mg tranexamic acid modified release tablets exhibited linear pharmacokinetics following repeated administration (7 days) of a 1.3 g dose under fasting conditions.

Steady-state plasma concentrations of tranexamic acid for the modified-release tablets were reached on Day 4 (−72-hour), since the p-value for the first contrast was not statistically significant at a 5% alpha error

The pharmacokinetics of tranexamic acid was properly described using a three compartment PK model with linear elimination. The absorption kinetic of the single-dose (Day 1) data of tranexamic acid for the MR formulation was best described using a mixed-order rate constant of absorption.

Plasma Pharmacokinetic Parameters for the modified release (MR) formulation of Tranexamic Acid on day 1 are listed in Table 21 below.

TABLE 21

	ln AUC_{0-t}* (mcg · h/ml)	ln AUC_{inf}* (mcg · h/ml)	ln C_{max}* (mcg/ml)	T_{max} (h)	Half-life (h)	K_{el} (l/h)
Mean	74.571	76.875	13.176041	3.079	11.078	0.06443
CV %	31.3	30.4	33.1	25.0	16.9	18.3
N	19	19	19	19	19	19

*For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported; AUC_{0-t} = AUC post dose (0-36 hours)

Plasma Pharmacokinetic Parameters for the modified release (MR) formulation of Tranexamic Acid on day 7 are listed in Table 22 below.

TABLE 22

	ln AUC_{τ}* (mcg · h/ml)	ln C_{max}* (mcg/mL)	ln C_{min}* (mcg/ml)	T_{max} (h)	Flux 1** (%)	Flux 2** (%)
Mean	74.791	15.803509	5.157681	2.553	113.16	219.21
CV %	29.0	30.1	31.2	14.4	21.6	44.6
N	19	19	19	19	19	19

*For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported; AUC_{τ} = AUC dosing interval (8 hours)
**Defined in Table 16

Menorrhagia Instrument

In clinical trials the primary goal is to obtain definitive evidence regarding the benefit to risk profile of the pharmacotherapy. One of the most challenging design tasks in studies of heavy menstrual bleeding which is a subjective complaint is the choice of efficacy endpoints or outcome measures. The Applicants have established two criteria for assessing the clinical relevance of the reduction in menstrual blood loss in the clinical efficacy studies. The first criterion was that the mean reduction in menstrual blood loss should be greater than 50 mL. The second criterion was based on the correlation between the reduction in menstrual blood loss and the subjects' perception of a meaningful symptomatic change, derived from blinded data from the measures of the Menorrhagia Instrument (MI) in the first treated menstrual period in the menstrual cycle during a controlled clinical study for safety and efficacy of tranexamic acid in heavy menstrual Bleeding. Analysis of the data for the symptomatic measures of the Menorrhagia Instrument (MI, measure six, FIG. **1**) established that a menstrual blood loss reduction of at least 36 mL as defined by the alkaline hematin test was regarded as meaningful by the clinical patients. The mean reduction in menstrual blood loss in patients treated with a tranexamic acid formulation at 1.9 and at 3.9 g/day met both criteria for a clinically meaningful result. Data from Menorrhagia Instrument (MI, measure six, FIG. **1**, which establishes that the treatment was meaningful to the patient provides the treating practitioner with an assessment of patient response to tranexamic acid therapy.

Example 7

Mennoraghia Impact Measure Validation

Objective measurements of menstrual blood loss are not practical in the healthcare setting, and they correlate poorly with a woman's subjective assessment of blood loss and its simpact on quality of life [Warner 2004; National Collaborating Centre for Women's and Children's Health, 2007]. Menorrhagia is a subjective condition and may be practically defined as menstrual loss that is greater than the woman feels that she can reasonably manage. The amelioration of symptoms of heavy menstrual loss are practical efficacy benefits of the treatment are therefore important to measure and validate in a controlled clinical environment.

The MI was evaluated in a sub population of patients enrolled in a clinical trial designed to assess the safety and efficacy of modified release tranexamic acid formulations (Example 1) at an oral dose of 3.9 g administered daily for up to 5 days during each menstrual period. Two groups of patients were used to assess the MI, one group of patients were those diagnosed with menorrhagia and undergoing treatment. The second group was an age matched normal group. The sub-study was designed: to collect sufficient quantitative data to support the construct-related validation of the MI measures; to collect sufficient quantitative data to support the assessment of meaningful/important change in blood loss to the women; to conduct a test/retest evaluation of the instrument, and to address the reliability of the MI measures.

Study Methods

Development of the MI began with a review of the literature focusing on the methods used to collect qualitative data from menorrhagia patients. Qualitative interviews with patients determined which symptomatic concepts were most important to women and could be included in a draft Impact Measure. Cognitive debriefing interviews to evaluate patient understanding of items led to the synthesis of a patient-based instrument for assessing the impact of limitations caused by heavy menstrual bleeding. Published measures were used in the evaluation of the psychometric properties of the Menorrhagia Instrument to assess Construct-Related Validity. The reference measures include, the Ruta Menorrhagia Questionnaire [Ruta 1995] and the Medical Outcomes Study Short-Form 36 Item Health Status Instrument (SF-36) [Ware 1992]. Scoring of the standardized measures followed published algorithms, Table 23.

TABLE 23

Descriptions of Instruments used in this study

Measure	Score Generated	Score Ranges
Menorrhagia Impact Measure (MI)	Blood Loss Severity (Q1)	1 (light) thru 4 (very heavy)
	Limitation	
	Work outside or inside the home (Q2)	1 (not at all) thru 5 (extremely)
	Physical activities (Q3)	1 (not at all) thru 5 (extremely)
	Social or leisure activities (Q4)	1 (not at all) thru 5 (extremely)
	Activity list (Q5)	[Descriptive]
	Change in blood loss (follow-up) (Q6, 6a, 6b)	[15-pt scale: 0 = no change, 1-7 improve, 1-7 worse]
	Meaningful/important change (Q6c)	Y/N
Ruta Menorrhagia Questionnaire	Global	0 (asymptomatic) - 42 (severe)
	Specific	
	Physical Function: Impact on work and daily activities (Q9 and Q10)	0 (asymptomatic) - 6 (severe)
	Social Function: Impact on social and leisure activities and sex-life (Q11 and Q12)	0 (asymptomatic) - 8 (severe)
SF-36	Physical Functioning, Role-Physical, Bodily Pain General Health (can be combined to form Physical Health Component Score); Vitality, Social Functioning, Role-Emotional, Mental Health (can be combined to form Mental Health Component Score)	0-100 (100 = minimal impairment)

Study Design

A total of 262 women completed the MI. The MI measures 1 through 5 were administered after subject's baseline period and after the subsequent first, second, third and sixth treatment periods. The MI measure 6 was administered after the first treatment period only. For this validation study, only the data collected through Month 1 of treatment was included in the analyses for the treatment cohort. The MI measures 1-5 were administered at baseline and at the subsequent first and second non-treatment periods for the subjects in the normal cohort The MI measure 6 was administered and data collected, at Month 1 and Month 2. The Ruta Menorrhagia Questionnaire, SF-36 Health Survey and the MIQ were completed by the subject before visit procedures were performed. A subset of at least 50 subjects were asked to return to the study site 7 to 10 days after the baseline Visit but before the next menstrual period starts to complete the MI a second time.

Treatment Group

A total of 177 patients were enrolled into the sub-study. During this time period 28 patients withdrew consent, dropped-out, or did not properly complete MI and were non-evaluable. The 149 patients remaining were intended to be age matched. The majority of patients in the study were in their late 30's or early 40's. Because of the difficulty of enrolling sufficient numbers of women with normal menstrual periods in this age bracket 18 evaluable patients were not age matched. A total of 131 evaluable patients were age matched. A sub-set of 80 evaluable patients participated in the test/retest segment of the validation. Of these patients 11 were evaluable but not age matched. Data from all 80 patients were used for statistical evaluation of the test/re-test correlations.

Normal Group

A group of women with self reported normal menstrual bleeding comprised the pool of normal women eligible for age matching in the study. A normal was defined as all of the following: a menstrual cycle between 26 and 32 days long, and their last (most recently completed) menstrual period was seven days or less in duration, the heaviest bleeding was three days or less, and the woman classified the bleeding overall as "light" or "moderate" as opposed to "heavy" or "very heavy. Women with normal periods who were enrolled into the study served as age-match controls for women recruited into the treatment group. Un-matching and re-matching occurred throughout the enrollment period if participants in either group dropped out of the study, if better re-matching increased the total number of matched pairs, or if the age-matched woman with normal periods did not enroll in the study.

Five women enrolled in the study did not complete the study through Visit 3. Another five women who did complete the study became 'unmatched' as the Treatment Group participant they had been matched to became non-evaluable. The 131 women who completed the study and remained matched are the Validation Sample Normal Group. A total of 51 women completed the Retest.

The following Measures were summarized and statistically analyzed:

- MI measure 1—Blood Loss Rating
- MI measure 2—Limitation of Work Outside or Inside the Home
- MI measure 3—Limitation of Physical Activities
- MI measure 4—Limitation of Social or Leisure Activities
- MI measure 6/6a/6b—Menstrual Blood Loss During Last Period
- MI measure 6c—Meaningfulness of Change in Menstrual Blood Loss

The statistics include the counts (missing data), mean, standard deviation, median, inter-quartile range, and minimum/maximum values. Differences in these variables between the treatment and normal cohorts were assessed using analysis of variance.

A p-value <0.05 was required for significance using two-sided hypothesis tests; no p-value adjustments were made for the analysis of multiple endpoints. All analyses were performed under SPSS version 11.5 for Windows, and the Stuart-Maxwell test for homogeneity was performed using Stata version 9.0 for Windows.

Validation of the MI was conducted using standardized analytic procedures found in the FDA Draft Guidance on Patient Reported Outcomes for Use in Evaluating Medical

Products for Labeling Claims and instrument review criteria developed by the Scientific Advisory Committee of the Medical Outcomes Trust.[1]

1 Scientific Advisory Committee of the Medical Outcomes Trust. Assessing health status and quality-of-life instruments: attributes and review criteria. Qual Life Res. 2002; 11: 193-205

Evaluation of the Menorrhagia Instrument

The MI consisted of 4 individual measures (1-4) that were analyzed separately for validation. No summative scale was derived. Measure 5, served as descriptive of variables and did not undergo standard validation analyses. Measures 6, 6a and 6b dealt with menstrual blood loss relative to the previous menstrual period. The answers to the measures in the subparts of measure 6, were combined to produce a 15 point rating scale. The scale values range from −7 to +7 with −7 representing a very great deal worse menstrual blood loss than the previous period, and +7 representing a very great deal better menstrual blood loss than the previous period. The midpoint (0) represents the perception of about the same menstrual blood loss as the previous period.

Test-retest reliability assessed if items produced stable, reliable scores under similar conditions (Guttman, 1945). Reproducibility was evaluated in a subset of at least 50 from the treatment group and at least 50 from the normal group 7 to 10 days after the baseline visit using the intra-class correlation coefficient (ICC, see formula below). Values above 0.70 indicated the stability of an instrument over time. The following formula was used to compute the Intraclass Correlation Coefficient (ICC):

$$ICC = \frac{A^2 + B^2 + C^2}{A^2 + B^2 + D^2 - \left(\frac{C^2}{n}\right)}$$

where:

A=Standard deviation of baseline score
B=Standard deviation of Time 2 score
C=Standard deviation of change in score
D=mean of change in score
n=number of respondents

The data for each of the measures was above 0.70. In the test population, n=88, values of 0.72 (0.60-0.81), 0.75 (0.64-0.83), 0.77 (0.67-0.84) and 0.76 (0.66-0.84) for measures 1 to 4 respectively. The aged matched normal values where n=51 were 0.77 (0.63-0.86), 0.67 (0.49-0.80), 0.75 (0.60-0.85) and 0.86 (0.77-0.92) respectively.

Construct-Related Validity was established when relationships among items, domains, and concepts conform to what was predicted by the conceptual framework for the instrument. This includes convergent, discriminant, and known-groups validity. Convergent and discriminant validity was present where measures of the same construct are more highly related and measures of different constructs were less related. To assess convergent and discriminant validity, Pearson's correlation coefficients were computed between each MI measure and items and scales from the SF-36 and the Ruta Menorrhagia Questionnaire included in the study design and administered at the same visit. The following hypotheses were tested:

The MI Blood Loss Measure (#1) will have a stronger association with the Ruta Menorrhagia Questionnaire (RMQ) than to the SF-36 subscales.

The MI Physical Activity Limitation Measure (#3) will have a stronger association with the RMQ Physical Function scale, the SF-36 Physical domain, the SF-36 Role-Physical domain, and SF-36 Physical Component Summary score than the Ruta Social, SF-36 Social, and SF-36 Vitality domains.

The MI Social/Leisure Activity Limitation will have a have stronger associations with the RMQ Social Function scale and the SF-36 Social Function domain than the RMQ Physical, the SF-36 Physical and SF-36 Bodily Pain domains.

For convergent validity, the correlations of MI measures with Ruta subscales, SF-36 subscales, and diary data are shown in Table 24. The Ruta global score was highly correlated with each MI measures (range 0.757-0.809). The correlations of items with the SF-36 subscales were low to moderate, which is to be expected since the SF-36 is not a disease-specific measure, but rather a more generic health status measure unable to detect differences between a normal population and a population of women with menorrhagia. The MI measures were more strongly correlated with the SF-36 Physical and Role Physical subscales than other SF-36 subscales.

TABLE 24

Correlations Between Menorrhagia Instrument Patient Reported Outcome (PRO) Measures and Ruta/SF-36/Diary

	MI measure 1 Blood Loss	MI measure 2 Limit work outside or inside home	MI measure 3 Limit physical activity	MI measure 4 Limit social or leisure activity
Ruta - Global	0.767 (0.000)	0.785 (0.000)	0.807 (0.000)	0.809 (0.000)
Ruta - Physical Fx	0.512 (0.000)	0.682 (0.000)	0.646 (0.000)	0.664 (0.000)
Ruta - Social Fx	0.606 (0.000)	0.634 (0.000)	0.659 (0.000)	0.683 (0.000)
SF-36 - Physical Fx	−0.229 (0.000)	−0.234 (0.000)	−0.264 (0.000)	−0.273 (0.000)
SF-36 - Social Fx	−0.118 (0.057)	−0.194 (0.002)	−0.200 (0.001)	−0.261 (0.000)
SF-36 - Role Physical	−0.200 (0.001)	−0.279 (0.000)	−0.258 (0.000)	−0.303 (0.000)
SF-36 - Vitality	−0.143 (0.021)	−0.193 (0.002)	−0.248 (0.000)	−0.250 (0.000)
SF-36 - Bodily Pain	−0.087 (0.163)	−0.168 (0.006)	−0.192 (0.002)	−0.205 (0.001)
SF-36 - PCS	−0.190 (0.002)	−0.271 (0.000)	−0.285 (0.000)	−0.275 (0.000)

The data supported the hypothesis that the MI Blood Loss measure (#1) had a stronger association with the Ruta global score than to the SF-36 subscales. While the hypothesis that MI measure #3 (Physical Activity Limitation) would be strongly associated to the physical domains of the RMQ (r=0.65) and SF-36 (r=−0.26) was confirmed, this measure was also strongly correlated to the RMQ Social Functioning (r=0.66). MI measure #4 (Social or Leisure Activity Limitation) was highly correlated to the RMQ Social (r=0.68) and moderately associated with the SF-36 Social Functioning domain.

Known-groups validity determined the ability of the instrument to discriminate between groups of subjects known to be distinct. The ability of the MI items to discriminate among known groups was assessed by comparing the 4 items (1 thru 4) to responses from the two groups (treatment and normal) at baseline. Differences in these variables, between the treatment and normal groups, were assessed using analysis of variance. A p-value <0.05 was required for significance using two-sided hypothesis tests; no p-value adjustments was made for the analysis of multiple endpoints.

For each MI measure, the mean score for the treatment group was significantly different than the mean score for the normal group (p<0.001). The treatment group scores were higher for each individual measure, indicating greater limitation as a result of their excessive menstrual blood loss (see Table 25).

TABLE 25

Known-Groups Validity of the MIQ

		Treatment Cohort			AGE MATCH NORMAL Cohort			
		N	Mean	St. Dev.	N	Mean	St. Dev.	F (sig.)[1]
MI measure 1	Self-perceived blood loss	131	3.25	0.61	131	2.10	0.61	234.727 (<0.001)
MI measure 2	Limit you in your work	131	3.04	0.99	131	1.34	0.59	286.864 (<0.001)
MI measure 3	Limit you in your physical activities	131	3.28	0.95	131	1.49	0.72	299.011 (<0.001)
MI measure 4	Limit you in your social/leisure activities	131	3.05	1.06	131	1.37	0.72	227.312 (<0.001)

The ability to detect change required that values for the item or instrument change when the concept it measures changed. In order to measure the MI items ability to detect change, longitudinal data were evaluated focusing primarily on the changes from baseline to month 1. Differences in proportions and comparisons between treatment and normal groups were compared using chi-square statistics (the Stuart-Maxwell test testing marginal homogeneity for all categories simultaneously). Cohen Effect Size statistics were also compared between the treatment and normal groups. The Cohen Effect Size was computed by taking the mean change in measure score (baseline to month 1) and dividing that by the standard deviation of mean baseline score[2].

2 Cohen, J. J. (1988). Statistical power analysis for the behavioral sciences (p. 8). Erlbaum: Hillsdale, N.J.

Ability to detect change was described for each item in Tables 26A-D by indicating the distribution of baseline and month 1 response option pairs for all patients. Change in responses from baseline to month 1 was tested using the Stuart-Maxwell test. For the treatment group, there was significant change in responses to each measure from baseline to month one (p<0.001). For the normal group, none of the items had significant changes in responses from baseline to month one. FIG. 8 illustrates the distribution of responses to measure 1 at baseline and at month one. In the treatment group, the proportion reporting light or moderate bleeding as measured with item 1, increased from baseline to month 1, and in the normal group this proportion changed very little.

TABLE 26A

Sensitivity to change of the MI Measure 1

			Month 1				
Cohort		Response category	Light	Moderate	Heavy	Very Heavy	Stuart-Maxwell test of association
Treatment	Baseline	Light	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	59.09 (p < 0.001)
		Moderate	0 (0.0%)	8 (6.3%)	4 (3.2%)	0 (0.0%)	
		Heavy	3 (2.4%)	41 (32.5%)	24 (19.0%)	2 (1.6%)	
		Very Heavy	2 (1.6%)	18 (14.3%)	13 (10.3%)	11 (8.7%)	
Normal	Baseline	Light	9 (6.9%)	5 (3.8%)	0 (0.0%)	0 (0.0%)	6.35 (p = 0.130)
		Moderate	12 (9.2%)	77 (59.2%)	4 (3.1%)	0 (0.0%)	

TABLE 26A-continued

Sensitivity to change of the MI Measure 1

Cohort	Response category	Month 1 Light	Moderate	Heavy	Very Heavy	Stuart-Maxwell test of association
	Heavy	0 (0.0%)	9 (6.9%)	8 (6.2%)	2 (1.5%)	
	Very Heavy	0 (0.0%)	2 (1.5%)	2 (1.5%)	0 (0.0%)	

TABLE 26B

Sensitivity to change of the MI Measure 2

Cohort		Response category	Month 1 Not at all	Slightly	Moderately	Quite a bit	Extremely	Stuart-Maxwell test of association
Treatment	Baseline	Not at all	5 (4.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	53.33 (p < 0.001)
		Slightly	12 (9.5%)	11 (8.7%)	2 (1.6%)	1 (0.8%)	0 (0.0%)	
		Moderately	17 (13.5%)	26 (20.6%)	14 (11.1%)	1 (0.8%)	0 (0.0%)	
		Quite a bit	2 (1.6%)	8 (6.3%)	5 (4.0%)	9 (7.1%)	0 (0.0%)	
		Extremely	3 (2.4%)	3 (2.4%)	3 (2.4%)	1 (0.8%)	1 (0.8%)	
Normal	Baseline	Not at all	89 (69.0%)	5 (3.9%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	2.86 (p = 0.517)
		Slightly	8 (6.2%)	13 (10.1%)	4 (3.1%)	2 (1.6%)	0 (0.0%)	
		Moderately	0 (0.0%)	3 (2.3%)	4 (3.1%)	0 (0.0%)	0 (0.0%)	
		Quite a bit	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
		Extremely	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

TABLE 26C

Sensitivity to change of the MI Measure 3

Cohort		Response category	Month 1 Not at all	Slightly	Moderately	Quite a bit	Extremely	Stuart-Maxwell test of association
Treatment	Baseline	Not at all	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	64.58 (p < 0.001)
		Slightly	12 (9.5%)	12 (9.5%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	
		Moderately	14 (11.1%)	20 (15.9%)	11 (8.7%)	3 (2.4%)	0 (0.0%)	
		Quite a bit	6 (4.8%)	17 (13.5%)	9 (7.1%)	5 (4.0%)	0 (0.0%)	
		Extremely	5 (4.0%)	2 (1.6%)	2 (1.6%)	3 (2.4%)	2 (1.6%)	
Normal	Baseline	Not at all	72 (55.4%)	9 (6.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.99 (p = 0.708)
		Slightly	14 (10.8%)	18 (13.8%)	3 (2.3%)	1 (0.8%)	0 (0.0%)	
		Moderately	0 (0.0%)	6 (4.6%)	4 (3.1%)	1 (0.8%)	0 (0.0%)	
		Quite a bit	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	
		Extremely	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

TABLE 26D

Sensitivity to change of the MI Measure 4

Cohort		Response category	Month 1: Not at all	Slightly	Moderately	Quite a bit	Extremely	Stuart-Maxwell test of association
Treatment	Baseline	Not at all	6 (4.8%)	3 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	60.77 (p < 0.001)
		Slightly	16 (12.7%)	10 (7.9%)	0 (0.0%)	2 (1.6%)	0 (0.0%)	
		Moderately	19 (15.1%)	14 (11.1%)	12 (9.5%)	2 (1.6%)	1 (0.8%)	
		Quite a bit	5 (4.0%)	14 (11.1%)	4 (3.2%)	6 (4.8%)	0 (0.0%)	
		Extremely	3 (2.4%)	4 (3.2%)	1 (0.8%)	3 (2.4%)	1 (0.8%)	
Normal	Baseline	Not at all	84 (64.6%)	11 (8.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.71 (p = 0.807)
		Slightly	10 (7.7%)	14 (10.8%)	2 (1.5%)	0 (0.0%)	0 (0.0%)	
		Moderately	0 (0.0%)	4 (3.1%)	2 (1.5%)	0 (0.0%)	0 (0.0%)	
		Quite a bit	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.5%)	0 (0.0%)	
		Extremely	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

The amount of change in each item from baseline to month 1 is shown in Table 27. For the treatment group, the mean change in response from baseline to month 1 ranged from −0.76 to −1.16 for the four items. The calculated effect size shows this amount of change for each item ranged from −0.9 to −1.2. For the normal group, the mean change in response from baseline to month 1 ranged from 0.03 to −0.12 for the four items. The effect size for each item ranged from 0.053 to −0.197. This analysis shows a large response in patients undergoing treatment and little to no response in normal women who have received no treatment. This instrument is capable of identifying the perceived improvement in menstrual blood loss.

Responses from treatment group participants were divided based on two separate responder definitions. In the first definition, a responder was a patient indicating a one-category change in MI measure 1. In the second definition, a responder was a patient who entered the study as "Very heavy" or "Heavy" (MI measure 1) and then, following treatment (month 1), indicated being "Moderate" or "Light". When the treatment group was analyzed using the first responder definition, 69 (90%) of the 77 responders reported improvement and 63 (91%) of these rated this improvement as "a meaningful change". Thirty-five (71%) of the 49 non-responders reported improvement and 35 (92%) rated their change as "a meaningful change".

TABLE 27

Sensitivity to Change of MI Effect Size

	Menorrhagia Item	BASELINE n	BASELINE Mean	BASELINE St Dev	MONTH 1 n	MONTH 1 Mean	MONTH 1 St Dev	CHANGE n	CHANGE Mean	CHANGE St Dev	Effect Size[1]
Item 1	Self-perceived blood loss	126	3.25	0.62	126	2.49	0.73	126	−0.76	0.84	−1.226
Item 2	Limit you in your work	126	3.05	0.99	126	2.12	0.99	126	−0.93	1.13	−0.939
Item 3	Limit you in your physical activities	126	3.29	0.95	126	2.13	1.00	126	−1.16	1.17	−1.221
Item 4	Limit you in your social/leisure activities	126	3.06	1.06	126	2.00	1.04	126	−1.06	1.19	−1.000

	Menorrhagia Item	BASELINE n	BASELINE Mean	BASELINE St Dev	CHANGE n	CHANGE Mean	n	Mean	St Dev	Effect Size
Item 1	Self-perceived blood loss	130	2.10	0.61	130	1.98	130	−0.12	0.56	−0.197
Item 2	Limit you in your work	129	1.32	0.57	129	1.35	129	0.03	0.50	0.053
Item 3	Limit you in your physical activities	130	1.49	0.72	130	1.43	130	−0.06	0.57	−0.083
Item 4	Limit you in your social/leisure activities	130	1.37	0.72	130	1.33	130	−0.04	0.58	−0.056

When the treatment group was analyzed using the second responder definition, 57 (89%) of the 64 responders reported improvement, and 52 (91%) reported their change to be meaningful. Forty-seven (76%) of the 62 non-responders reported improvement, and 45 (90%) reported their change to be meaningful. Among the normal group, 96 (73%) of 130 patients reported no change. Twenty-one (16%) reported improvement, and 13 (10%) reported worsening. Of the patients reporting change, 15 (44%) rated the change as "a meaningful change".

For those women on treatment who reported a meaningful improvement (78.6%), MI items 3 and 4 showed the greatest treatment effect with improvements of 1.29 and 1.17, respectively. As expected, the majority of the Normal cohort (73.3%) reported no change in their menstrual period.

Example 8

The following clinical study was carried out in order to evaluate the efficacy and safety of tranexamic acid provided as an oral modified release formulation of Example 1 to reduce menstrual blood loss (MBL) in women with menorrhagia when administered during menstruation compared to placebo.

This was a multi-center, double-blind, placebo-controlled, parallel-group study. The study consisted of a screening phase of two (2) menstrual periods (no treatment) to determine eligibility, followed by a treatment phase spanning three (3) menstrual periods to assess the efficacy and safety of tranexamic acid during menstruation.

The primary objective of the study was to determine the efficacy of a 1.95 gm/day of tranexamic acid (650 mg orally three times daily, TID) and 3.9 gm/day of tranexamic acid (1.3 gm orally three times daily, TID) administered during menstruation for up to 5 days (maximum of 15 doses) to reduce menstrual blood loss in women with objective evidence of heavy menstrual bleeding.

The secondary objective of the study was to determine the improvement with administration of 1.95 gm/day or 3.9 gm/day of tranexamic acid in women with heavy menstrual bleeding in their symptoms including, Limitation in Social Leisure Activities (LSLA) and Limitation in Physical Activities (LPA) scores from the Menorrhagia Instrument Measures (FIG. 7). Further the objective was to determine the safety of the 1.95 gm/day and 3.9 gm/day of the modified release tranexamic acid formulation administered during menstruation.

Three treatment periods were averaged for the menstrual blood loss (MBL) primary efficacy evaluation (first, second, and third periods on treatment). All periods were evaluated for the secondary endpoints, and for safety of tranexamic acid at an oral dose of 1.3 gm or placebo administered three (3) times daily for up to five consecutive (5) days (maximum of 15 doses) during menstruation.

Criteria for Evaluation (Safety and Efficacy Assessments)

Efficacy Assessment

Menstrual blood loss (MBL) was assessed during the entire menstrual period by the alkaline hematin test (AHT) method. The Menorrhagia Instrument Measures (FIG. 7) were also administered immediately after each menstrual period under investigation. For the Primary Endpoint, the objective reduction in menstrual blood loss (MBL) during the entire menstrual period as assessed by the AHT Method was assessed.

For the Secondary Endpoints, the scores for Limitation in Social Leisure Activities (LSLA) and the scores for Limitation in Physical Activities (LPA) from the Menorrhagia Instrument Measures (MI), measures #4 and #3, respectively) were assessed.

For the Secondary Endpoints the data collected included at least; Menstrual Blood Loss (MBL) assessment score (MI measure 1), Limitation in Work Outside or Inside the Home (LWH) score (MI item 2), and subject assessment of meaningfulness score from the MI (measure 6) (used for the MBL responder analysis).

Efficacy Results

The efficacy results were based on the modified ITT (mITT) populations. Results from the analysis of other populations were very similar to those derived from the analysis of the mITT population, and do not alter the general conclusions presented below. The numbers of subjects in the mITT populations in the efficacy study are summarized in Table 28 below:

TABLE 28

Numbers of Subjects in mITT Populations in Pivotal Efficacy Studies

Treatment	N
Placebo	67
Tranexamic acid (1.95 g/day)	115
Tranexamic acid (3.9 g/day)	112

Primary Efficacy Endpoint

Subjects in both treatment groups experienced a significant reduction from baseline in mean MBL The mean reduction in MBL in subjects treated with the higher dose (3.9 g/day) was 65.3 mL, or 38.6% compared with the baseline value ($p<0.0001$). A smaller reduction was observed in subjects at the lower dose of 1.95 g/day (46.5 mL, 26.1%, $p<0.0001$). The reductions in both groups were statistically significant ($p<0.0001$) when compared with that in the placebo control group (2.98 mL).

Key Secondary Efficacy Endpoints

Significant treatment-related reductions from baseline in mean LSLA score and mean LPA score were observed. Other secondary efficacy endpoints provided supportive evidence of the efficacy of tranexamic acid. Specifically, subjects' assessments of MBL (MI item 1) and LWH (MI measure 2), were both significantly reduced for subjects in the 3.9 g/day tranexamic acid group compared with placebo. The number of patients responding to treatment was assessed. A responder was defined as a subject with a reduction in MBL and a subjective "meaningful" improvement according to the MI (measure 6c) after the first menstrual cycle during the treatment period. The proportion of responders in this study was 58.3% and 71.0% in the 1.95 and 3.9 g/day tranexamic acid groups respectively, compared with placebo response rate of 23.4% ($p<0.0001$ for both dose levels).

These results demonstrate that tranexamic acid at doses of 1.9 and 3.9 g/day ameliorates the symptoms associated with HMB, including at least limitations in social, leisure, and physical functioning. In addition, these results provide converging evidence that tranexamic acid modified-release tablets are efficacious in the treatment of HMB.

Heavy Menstrual Bleeding in Patients with Fibroids Included in Clinical Study of this Example

Analyses was initiated to assess tranexaminc acid modified release tablets treatment effect stratified by the presence of fibroids at baseline. The primary goal of this analysis was to evaluate treatment-by-fibroids effect across variety of end-points. The results of the analysis is found in the following Tables:

TABLE 29.1

Treatment-Induced Changes in MBL (mL) over Three Cycles of Therapy Stratified by the Presence of Fibroids MITT Population

		Baseline MBL (mL)		Change in MBL from Baseline (mL)		Percent Change in MBL from Baseline (mL)	
Treatment	Statistics	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids
Lysteda 3.9	N Mean	50	64	49	63	49	63
	(SD)	192 (93)	149 (68)	−80 (57)	−54 (43)	−41 (18)	−38 (25)
	Median	172	129	−67	−51	−37	−43
Lysteda	N Mean	44	72	44	71	44	71
1.95	(SD)	211 (151)	157 (73)	−45 (69)	−47 (49)	−22 (31)	−27 (23)
	Median	157	126	−38	−43	−26	−31
Placebo	N Mean	24	43	24	43	24	43
	(SD)	180 (93)	139 (43)	−5 (66)	−2 (31)	+2 (25)	0 (25)
	Median	147	128	0	−2	0	−1

NOTE:
MEAN values for baseline cycles and in-treatment cycles are used in these calculations

TABLE 29.2

Treatment-Induced Changes in MBL (mL) over Three Cycles of Therapy Stratified by the Presence of Fibroids MITT Population

		Baseline MBL (mL)		Change in MBL from Baseline (mL)		Percent Change in MBL from Baseline (mL)	
Treatment	Statistics	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids
Lysteda 3.9	N Mean	50	64	142	179	142	179
	(SD)	192 (93)	149 (68)	−79 (59)	−54 (49)	−41 (21)	−38 (29)
	Median	172	129	−68	−55	−41	−43
Lysteda	N Mean	44	72	125	209	125	209
1.95	(SD)	211 (151)	157 (73)	−50 (79)	−48 (56)	−25 (34)	−27 (30)
	Median	157	126	−45	−45	−29	−33
Placebo	N Mean	24	43	70	124	70	124
	(SD)	180 (93)	139 (43)	−1 (74)	−3 (42)	+3 (34)	−1 (32)
	Median	147	128	+3	0	+1	0

NOTE:
MEAN baseline values are compared to the individual in-treatment cycles

TABLE 29.3

Percent of Subjects Reaching Specified MBL Reduction Targets over Three Cycles of Therapy Stratified by the Presence of Fibroids MITT Population

		Percent of subjects with >36 mL reduction in MBL		Percent of subjects with >50 mL reduction in MBL		Percent of subjects reaching normal range (<=80 mL)	
Treatment	Statistics	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids
Lysteda 3.9	n/N (%)	45/53 (84.9%)	48/67 (71.6%)	35/53 (66.0%)	37/67 (55.2%)	20/53 (37.7%)	39/67 (58.2%)*
Lysteda 1.95	n/N (%)	24/45 (53.3%)	41/73 (56.2%)	19/45 (42.2%)	30/73 (41.1%)	9/45 (20.0%)	24/73 (32.9%)

TABLE 29.3-continued

Percent of Subjects Reaching Specified MBL Reduction Targets over Three Cycles of Therapy Stratified by the Presence of Fibroids MITT Population

		Percent of subjects with >36 mL reduction in MBL		Percent of subjects with >50 mL reduction in MBL		Percent of subjects reaching normal range (<=80 mL)	
Treatment	Statistics	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids
Placebo	n/N (%)	1/24 (4.2%)	8/45 (17.8%)	1/24 (4.2%)	5/45 (11.1%)	4/24 (16.7%)	8/45 (17.8%)

NOTE:

MEAN values for baseline cycles and in-treatment cycles are used in these calculations

TABLE 29.4

Percent of Subjects Reaching Specified MBL Reduction Targets for All Cycles of Therapy Stratified by the Presence of Fibroids MITT Population

		Percent of subjects with >36 mL reduction in MBL			Percent of subjects with >50 mL reduction in MBL			Percent of subjects reaching normal range (<=80 mL)		
Treatment	Statistics	With Fibroids	Without Fibroids	Total	With Fibroids	Without Fibroids	Total	With Fibroids	Without Fibroids	Total
Lysteda 3.9	n/N (%)	115/147 (78.2%)	129/189 (68.3%)	244/336 (72.6%)	94/147 (64.0%)	105/189 (55.6%)	199/336 (59.2%)	59/147 (40.1%)	106/189 (56.1%)	165/336 (49.1%)
Lysteda 1.95	n/N (%)	81/132 (61.4%)	127/213 (59.6%)	208/345 (60.3%)	65/132 (49.2%)	91/213 (42.7%)	156/345 (45.2%)	37/132 (28.0%)	79/213 (37.1%)	116/345 (33.6%)
Placebo	n/N (%)	13/72 (18.1%)	29/129 (22.5%)	42/201 (20.9%)	10/72 (13.9%)	21/129 (16.3%)	31/201 (15.4%)	13/72 (18.1%)	26/129 (20.2%)	39/201 (19.4%)

NOTE:

MEAN baseline values are compared to the individual in-treatment cycles

TABLE 30

Treatment-Induced Changes in MIQ Q1 over Three Cycles of Therapy Stratified by the Presence of Fibroids MITT Population

		Baseline Q1		Post-Baseline Q1		Change in Q1 from Baseline	
Treatment	Statistics	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids
Lysteda 3.9	N Mean	49	63	49	63	49	63
	(SD)	2.92	2.71	2.27	2.19	−0.65	−0.53
	Median	(0.61)	(0.63)	(0.57)	(0.71)	(0.70)	(0.80)
		3.0	2.5	2.33	2.0	−0.67	−0.5
Lysteda 1.95	N Mean	44	71	44	71	44	71
	(SD)	2.80	2.82	2.40	2.39	−0.39	−42
	Median	(0.63)	(0.56)	(0.67)	(0.62)	(0.60)	(0.65)
		3.0	3.0	2.33	2.33	−0.33	−0.5
Placebo	N Mean	24	42	24	42	24	42
	(SD)	2.85	2.79	2.67	2.74	−0.18	−0.05
	Median	(0.52)	(0.61)	(0.54)	(0.53)	(0.53)	(0.84)
		3.0	3.0	2.67	2.67	+0.25	0.0

TABLE 30.1

Treatment-Induced Changes in MIQ Q2 over Three Cycles of Therapy
Stratified by the Presence of Fibroids
MITT Population

		Baseline Q2		Post-Baseline Q2		Change in Q2 from Baseline	
Treatment	Statistics	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids
Lysteda 3.9	N Mean	49	63	49	63	49	63
	(SD)	3.15	2.99	2.17	2.07	−0.99	−0.92
	Median	(0.90)	(1.01)	(0.94)	(0.96)	(0.87)	(1.08)
		3.0	3.0	2.0	2.0	−1.0	−0.83
Lysteda 1.95	N Mean	44	71	44	71	44	71
	(SD)	2.98	2.82	2.38	2.27	−0.59	−0.56
	Median	(1.05)	(0.56)	(0.86)	(0.94)	(0.80)	(0.97)
		3.0	3.0	2.33	2.33	−0.67	−0.67
Placebo	N Mean	24	42	24	42	24	42
	(SD)	2.98	2.69	2.78	2.49	−0.19	−0.20
	Median	(0.85)	(0.92)	(0.84)	(0.92)	(0.85)	(0.76)
		3.0	2.75	2.67	2.42	0.0	−0.17

TABLE 30.2

Treatment-Induced Changes in MIQ Q3 over Three Cycles of Therapy
Stratified by the Presence of Fibroids
MITT Population

		Baseline Q3		Post-Baseline Q3		Change in Q3 from Baseline	
Treatment	Statistics	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids
Lysteda 3.9	N Mean	49	63	49	63	49	63
	(SD)	3.17	2.98	2.13	2.07	−1.05	−0.92
	Median	(1.06)	(1.02)	(0.93)	(0.96)	(0.93)	(1.10)
		3.0	3.0	2.0	2.0	−1.0	−0.67
Lysteda 1.95	N Mean	44	71	44	71	44	71
	(SD)	2.92	3.01	2.36	2.24	−0.56	−0.77
	Median	(1.09)	(0.90)	(0.81)	(0.97)	(0.80)	(0.94)
		3.0	3.0	2.33	2.00	−0.58	−0.83
Placebo	N Mean	24	42	24	42	24	42
	(SD)	3.15	2.86	2.72	2.60	−0.42	−0.26
	Median	(0.88)	(0.85)	(0.90)	(0.90)	(0.78)	(0.81)
		3.0	3.0	2.67	2.67	−0.42	0.0

TABLE 30.3

Treatment-Induced Changes in MIQ Q4 over Three Cycles of Therapy
Stratified by the Presence of Fibroids
MITT Population

		Baseline Q3		Post-Baseline Q3		Change in Q3 from Baseline	
Treatment	Statistics	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids
Lysteda 3.9	N Mean	49	63	49	63	49	63
	(SD)	3.08	2.93	2.00	1.97	−1.08	−0.96
	Median	(1.11)	(1.05)	(0.92)	(1.05)	(1.10)	(1.13)
		3.0	3.0	2.0	1.67	−1.0	−0.83
Lysteda 1.95	N Mean	44	71	44	71	44	71
	(SD)	2.98	2.89	2.28	2.13	−0.70	−0.76
	Median	(1.05)	(0.97)	(0.82)	(0.94)	(0.83)	(0.98)
		3.0	3.0	2.33	2.00	−0.67	−0.83
Placebo	N Mean	24	42	24	42	24	42
	(SD)	3.06	2.73	2.68	2.40	−0.38	−0.32
	Median	(0.95)	(0.98)	(0.83)	(0.91)	(0.83)	(0.86)
		3.5	2.75	2.67	2.33	−0.33	−0.17

TABLE 30.5

Treatment-Induced Changes in MIQ Q6A-B at Cycle 1
Stratified by the Presence of Fibroids
MITT Population

		Change in Q6A-B from Baseline		
Treatment	Statistics	With Fibroids	Without Fibroids	Total
Lysteda 3.9	N	46	59	105
	Mean(SD)	4.1 (2.4)	3.1 (3.5)	3.5 (3.1)
	Median	5.0	3.0	4.0
Lysteda	N	42	67	109
1.95	Mean(SD)	2.8 (2.4)	2.7 (3.2)	2.7 (2.9)
	Median	3.0	3.0	3.0
Placebo	N	24	40	64
	Mean(SD)	−0.3 (3.6)	0.8 (3.8)	0.4 (3.8)
	Median	0	0	0

NOTE:
MIQ items 6, 6a and 6b are combined into one scale ranging from −7 to +7. There are very strong reasons for this approach.

Example 9

The following clinical study was carried out in order to evaluate the efficacy and safety of the modified release (MR) oral formulation of tranexamic acid of Example 1 to reduce menstrual blood loss (MBL) in women with menorrhagia when administered during menstruation compared to placebo.

This was a multi-center, double-blind, placebo-controlled, parallel-group study. The study consisted of a screening phase of two (2) menstrual periods (no treatment) to determine eligibility, followed by a treatment phase spanning six (6) menstrual periods to assess the efficacy and safety of tranexamic acid during menstruation.

The primary objective of the study was to determine the efficacy of a 3.9 gm/day (1.3 gm orally three times daily, TID) administered during menstruation for up to 5 days (maximum of 15 doses) to reduce menstrual blood loss in women with objective evidence of heavy menstrual bleeding.

The secondary objective of the study included an evaluation of the improvement observed from 3.9 gm/day of the modified release tranexamic acid formulation administered during menstruation in women with heavy menstrual bleeding on Limitation in Social Leisure Activities (LSLA)(item 4) and Limitation in Physical Activities (LPA) (MI measure #3) scores from the Menorrhagia Instruments (FIG. 7). Four treatment periods were averaged for the menstrual blood loss (MBL) primary efficacy evaluation (first, second, third and sixth periods). All periods were evaluated for the secondary endpoints, the secondary endpoints, and for safety of tranexamic acid at an oral dose of 1.3 gm or placebo administered three (3) times daily for up to five consecutive (5) days (maximum of 15 doses) during menstruation.

Criteria for Evaluation

Menstrual blood loss (MBL) was assessed during the entire menstrual period by the alkaline hematin test (AHT) method. Measures from the Menorrhagia Instrument (FIG. 7) were also administered immediately after each menstrual period under investigation. Subjects reported large stains exceeding the capacity of sanitary protection (and other patient reported outcome [PRO] items) during the menstrual period in daily diaries.

For the Primary Endpoint, the objective reduction in menstrual blood loss (MBL) during the entire menstrual period as assessed by the AHT Method was assessed.

For the Secondary Endpoints, the Limitation in Social Leisure Activities (LSLA) and the Limitation in Physical Activities (LPA) scores from the Menorrhagia Instrument (MI measures #4 and #3, respectively) and the total number of large stains responder analysis during the menstrual period from subject diaries were assessed.

For the Secondary Endpoints, assessment of the following were included, Menstrual Blood Loss (MBL) assessment score (MI measure #1), Limitation in Work Outside or Inside the Home (LWH) score (MI measure #2), and subject assessment of meaningfulness score from the MI (Measure #6) (used for the MBL responder analysis).

Efficacy Results

The efficacy results were based on the modified ITT (mITT) populations. The numbers of subjects in the mITT populations in the efficacy study are summarized in the Table below:

TABLE 31

Numbers of Subjects in mITT Populations in Pivotal Efficacy Studies

Treatment	N
Placebo	72
Tranexamic acid (3.9 g/day)	115

Primary Efficacy Endpoint

Subjects experienced a significant reduction from baseline in mean MBL. The mean reduction in MBL in the tranexamic acid-treated subjects was 69.6 mL, or 40.4% compared with the baseline value ($p<0.0001$). The reduction in MBL was also statistically significant ($p<0.0001$) when compared with that in the placebo control group (12.6 mL, 8.2%).

Secondary Efficacy Endpoints

For the secondary efficacy endpoints, significant treatment-related reductions from baseline in mean LSLA score and mean LPA score were observed. Subjects' assessments of MBL (MI measure #1) and LWH (MI measure #2), were both significantly reduced for subjects in the 3.9 g/day tranexamic acid group compared with placebo.

The number of patients responding to treatment was assessed as described in the previous example. A responder was defined as a subject with a reduction in MBL and a subjective "meaningful" improvement according to the MI (measure #6c) after the first menstrual cycle during the treatment period. The proportion of responders increased in the 3.9 g/day tranexamic acid treatment group (65.4%) compared with the placebo group (31.8%, $p<0.0001$). These results demonstrate that 3.9 g/day tranexamic acid ameliorates the symptoms associated with HMB, including improvement in limitations in social, leisure, and physical functioning. In addition, these results provide converging evidence that tranexamic acid modified-release tablets are efficacious in the treatment of HMB.

In both the Example 9 and Example 10 studies, the reduction in menstrual blood loss (MBL) was evident in the first menstrual period after commencing treatment with 3.9 g/day tranexamic acid. The response to treatment was maintained for the duration of the study (three and six menstrual cycles in Example 9 and Example 10 respectively; Regression analysis in the study of Example VIII confirmed that the response to

tranexamic acid was durable over the six menstrual cycles (regression slope of −0.90 mL/cycle, p=0.615).

Summary of Clinical Findings from the Studies of Examples 8 and 9

The efficacy and safety of the tranexamic acid (TXA MR) modified release tablets in the treatment of HMB was demonstrated in one 3-cycle treatment and one 6-cycle treatment, randomized, double-blind, placebo-controlled study. In these studies, the primary outcome measure was menstrual blood loss (MBL), measured using a validated menstrual blood loss method. The key secondary outcome measures were based on responses to items on the Menorrhagia Instrument (MI), a validated disease-specific patient-reported outcome instrument that measured Limitations in Social or Leisure activities and Limitations in Physical Activities. Large stains (soiling beyond the undergarment) and sanitary product use were also included as secondary outcome measures. In these studies, subjects were 18 to 49 years of age with a mean age of approximately 40 years and a BMI of approximately 32 kg/m2. On average, subjects had an HMB history of approximately 10 years and 40% had fibroids as determined by transvaginal ultrasound. About 20% were smokers and approximately 50% reported using alcohol. Approximately 70% were Caucasian, 25% were Black, and 5% were Asian, Native American, Pacific Islander, or Other. Seven percent (7%) of subjects were of Hispanic origin. In addition, approximately 18% of subjects were taking multivitamins and 7% of subjects were taking iron supplements.

Three-Cycle Treatment Study

This study compared the effects of two doses of tranexamic acid modified release tablets (1.95 g and 3.9 g given daily for up to 5 days during each menstrual period) versus placebo on MBL over a 3-cycle treatment duration. A total of 304 patients (117 TXA MR 1.95 g/day, 118 TXA MR 3.9 g/day, 69 Placebo) were randomized. MBL was significantly reduced in patients treated with 3.9 g/day TXA MR compared to placebo (mean 3.9 g/day TXA MR=65.31 mL [percent MBL reduction=38.6%]; placebo mean=2.98 mL [percent MBL reduction=1.9%]; p<0.0001). This reduction met the criteria for being a clinically meaningful improvement (MBL≧50 mL) and a meaningful improvement to women who participated in the trial (MBL≧36 mL). The 1.95 g/day dose did not meet the clinically meaningful improvement criteria for efficacy thereby establishing 3.9 g/day TXA MR as the minimally effective dose.

Tranexamic acid modified release tablets also significantly reduced limitations on social, leisure, and physical activities as measured by questions on the MI, and sanitary products used in the 3.9 g/day dose group compared to placebo (see Table32). No significant treatment differences were observed in response rates on the number of large stains.

TABLE 32

Secondary Outcomes in 3-Cycle Study

Outcome Measure	N	Mean (SD) Reduction*	P-value vs. Placebo
Social and Leisure Activities (MI)			
3.9 gm/day TXA MR	112	1.10 (1.12)	<0.0001
Placebo	66	0.34 (0.85)	
Physical Activities (MI)			
3.9 gm/day TXA MR	112	0.97 (1.03)	<0.0001
Placebo	66	0.32 (0.80)	
Sanitary Products Used			
3.9 gm/day TXA MR	112	6.36 (6.80)	<0.0001
Placebo	67	2.40 (6.13)	
Reduction in Large Stains**			
3.9 gm/day TXA MR	111	71 (64.0)	0.156
Placebo	67	35 (52.2)	

*Positive means reflect a decrease from baseline

**The reduction in large stains is reported as the number (%) of women who were classified as responders (i.e., subjects who experienced a positive change from baseline)

Six-Cycle Treatment Study

This study compared the effects of one dose of TXA MR (3.9 g/day) versus placebo on MBL over a 6-cycle treatment duration. A total of 196 patients (123 TXA MR 3.9 g/day, 73 Placebo) were randomized. Replicating the results from the 3-cycle treatment study, MBL was significantly reduced in patients treated with 3.9 g/day TXA MR compared to placebo (mean 3.9 g/day TXA MR=69.6 mL [percent MBL reduction=40.4%]; placebo mean=12.6 mL [percent MBL reduction=8.2%]; p<0.0001). This reduction met the criterion for being a clinically meaningful improvement (MBL≧50 mL) and a meaningful improvement to women (MBL≧36 mL). Limitations on social, leisure, and physical activities were also significantly reduced in the 3.9 g/day TXA MR dose group compared to placebo (see Table 33). No significant treatment differences were observed in sanitary products used or in response rates on the number of large stains.

TABLE 33

Secondary Outcomes in 6-Cycle Study

Outcome Measure	N	Mean (SD) Reduction*	P-value vs. Placebo
Social and Leisure Activities (MI)			
3.9 gm/day TXA MR	115	0.89 (0.85)	<0.0001
Placebo	72	0.38 (0.82)	
Physical Activities (MI)			
3.9 gm/day TXA MR	115	0.90 (0.86)	<0.0001
Placebo	72	0.35 (0.90)	
Sanitary Products Used			
3.9 gm/day TXA MR	115	5.20 (6.39)	0.129
Placebo	72	4.03 (5.94)	
Reduction in Large Stains**			
3.9 gm/day TXA MR	115	66 (57.4)	0.453
Placebo	72	37 (51.4)	

*Positive means reflect a decrease from baseline

**The reduction in large stains is reported as the number (%) of women who were classified as responders (i.e., subjects who experienced a positive change from baseline)

Example 10

Additional Pharmacokinetics

The pharmacokinetics of the modified release tranexamic acid tablets of Example 1 were further evaluated. After oral administration peak plasma levels (C_{max}) occurred at approximately 3 hours (T_{max}). The systemic bioavailability of the tablets in women aged 18-49 was approximately 45%. The mean C_{max} and the area under the plasma concentration curve (AUC) remained unchanged after repeated (1.3 gm TID) oral dosing for 5 days as compared to a single 1.3 gm oral dose.

The C_{max} and AUC after administration of a single 1.3 gm dose of tranexamic modified release tablets increased by 7% and 15% after food intake compared to fasting conditions, respectively. Therefore, the modified release tranexamic acid tablets can be taken with food.

The pharmacokinetic profile of the modified release tranexamic acid tablets was determined in 39 healthy women following a single 1.3 gm oral dose compared to repeated doses of 1.3 gm TID for 5 days. The results are shown in Table 34.

TABLE 34

Parameter	1 day	5 days
Dose	1.3 gm	1.3 gm TID[a]
AUC (mcg * h/L)	74.6[b]	74.8[c]
Coefficient of variation	33%	30%
C_{max} (mg/L)	13.2	15.8 (5.2[d])
T_{max} (h)	3.1	2.6
$T_{1/2}$ (h)[e]	11.1	N/A

Note:
Values represent geometric means, except Tmax which is the arithmetic mean.
[a]Dosed every 8 hours (3.9 g/day)
[b]AUC_{0-t}
[c]AUC_{t}
[d]C_{min} corresponding steady-state concentration
[e]Reflects terminal half-life

CONCLUSION

While the invention herein disclosed has been described by means of specific embodiments and applications thereof, numerous modifications and variations could be made thereto by those skilled in the art without departing from the spirit and scope of the present invention. Such modifications are understood to be within the scope of the appended claims.

In the preceding specification, the invention has been described with reference to specific exemplary embodiments and examples thereof. It will, however, be evident that various modifications and changes may be made thereto without departing from the broader spirit and scope of the invention as set forth in the claims that follow. The specification and drawings are accordingly to be regarded in an illustrative manner rather than a restrictive sense.

What is claimed is:

1. A tranexamic acid tablet formulation, comprising:
tranexamic acid or a pharmaceutically acceptable salt thereof; and
a modified release material, wherein the modified release material comprises a polymer selected from the group consisting of hydroxyalkylcelluloses, alkylcelluloses, cellulose ethers, partial esters thereof, and mixtures thereof;
wherein the modified release material is present in the formulation in an amount from about 10% to about 35% by weight of the formulation;
wherein the formulation provides an in-vitro dissolution release rate of the tranexamic acid or pharmaceutically acceptable salt thereof, when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C., of less than about 70% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, and about 100% by weight tranexamic acid or pharmaceutically acceptable salt thereof released by about 120 minutes; and
wherein each tablet of the formulation provides a dose of about 650 mg of tranexamic acid.

2. The tranexamic acid formulation of claim **1**, wherein the formulation provides a mean in-vitro dissolution release rate of the tranexamic acid or pharmaceutically acceptable salt thereof, when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C., of about 15% to about 29% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, about 56% to about 69% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, and about 89% to about 100% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes.

3. The tranexamic acid tablet formulation of claim **1**, wherein the tablet is a matrix tablet which comprises a pre-granulated drug mixed together with the modified release material.

4. The tranexamic acid tablet formulation of claim **1**, wherein the modified release material comprises a hydroxyalkylcellulose or a cellulose ether.

5. The tranexamic acid tablet formulation of claim **1**, wherein the modified release material comprises hydroxypropylmethylcellulose.

6. The tranexamic acid tablet formulation of claim **1**, wherein the modified release material is present in an amount of about 15% by weight of the formulation.

7. The tranexamic acid tablet formulation of claim **5**, wherein the modified release material is present in an amount of about 15% by weight of the formulation.

8. The tranexamic acid tablet formulation of claim **1**, wherein a single administration of the formulation comprising a dose of 1300 mg of tranexamic acid provides a mean maximum plasma concentration (C_{max}) of tranexamic acid in a range from about 9 mcg/ml to about 14.5 mcg/ml following the administration.

9. The tranexamic acid tablet formulation of claim **1**, wherein administration of the formulation comprising a dose of 1300 mg of tranexamic acid three times daily provides a mean maximum plasma concentration (C_{max}) of tranexamic acid in a range from about 12.5 mcg/ml to about 25 mcg/ml after multi-dose administration.

10. The tranexamic acid tablet formulation of claim **1**, wherein said formulation provides a mean T_{max} at from about 2 hours to about 3.5 hours after single dose oral administration.

11. A tranexamic acid tablet formulation, comprising:
tranexamic acid or a pharmaceutically acceptable salt thereof; and
an effective amount of a modified release material, wherein the modified release material comprises a polymer selected from the group consisting of hydroxyalkylcelluloses, alkylcelluloses, cellulose ethers, partial esters thereof, and mixtures thereof;
wherein the modified release material is present in the formulation in an amount from about 10% to about 35% by weight of the formulation;
wherein the formulation releases from about 10% to about 25% by weight tranexamic acid or pharmaceutically acceptable salt thereof every 15 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. such that about 100% of tranexamic acid or pharmaceutically acceptable salt thereof is released by about 120 minutes; and
wherein each tablet of the formulation provides a dose of about 650 mg of tranexamic acid.

12. The tranexamic acid tablet formulation of claim **1**, wherein administration of the formulation comprising a dose

of 1300 mg of tranexamic acid three times daily provides a mean maximum plasma concentration (C_{max}) of about 10 mcg/ml to about 20 mcg/ml after multi-dose administration.

13. The tranexamic acid tablet formulation of claim **1**, wherein a single administration of the formulation comprising a dose of 1300 mg of tranexamic acid provides a mean maximum plasma concentration (C_{max}) of tranexamic acid in a range from about 9 mcg/ml to about 17.5 mcg/ml.

14. The tranexamic acid tablet formulation of claim **5**, wherein the hydroxypropylmethylcellulose is present in an amount of about 10% to about 35% by weight of the formulation.

15. The tranexamic acid tablet formulation of claim **14**, wherein the hydroxypropylmethylcellulose is present in an amount of about 15% by weight of the formulation.

16. A tranexamic acid tablet formulation, comprising:

tranexamic acid or a pharmaceutically acceptable salt thereof; and

hydroxypropylmethylcellulose in an amount from about 10% to about 35% by weight of the formulation;

wherein the formulation provides an in-vitro dissolution release rate of the tranexamic acid or pharmaceutically acceptable salt thereof, when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C., of less than about 70% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, and about 100% by weight tranexamic acid or pharmaceutically acceptable salt thereof released by about 120 minutes; and

wherein each tablet of the formulation provides a dose of about 650 mg of tranexamic acid.

17. The tranexamic acid tablet formulation of claim **16**, wherein the hydroxypropylmethylcellulose is present in an amount of about 15% by weight of the formulation.

18. A tranexamic acid tablet formulation according to claim **11**, comprising:

tranexamic acid or a pharmaceutically acceptable salt thereof; and

hydroxypropylmethylcellulose in an amount from about 10% to about 35% by weight of the formulation;

wherein the formulation releases from about 10% to about 25% by weight tranexamic acid or pharmaceutically acceptable salt thereof every 15 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. such that about 100% of tranexamic acid or pharmaceutically acceptable salt thereof is released by about 120 minutes; and

wherein each tablet of the formulation provides a dose of about 650 mg of tranexamic acid.

19. The tranexamic acid tablet formulation of claim **18**, wherein the hydroxypropylmethylcellulose is present in an amount of about 15% by weight of the formulation.

* * * * *

US008022106B2

(12) **United States Patent**
Moore et al.

(10) **Patent No.: US 8,022,106 B2**
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(54) **TRANEXAMIC ACID FORMULATIONS**

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See application file for complete search history.

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(57) **ABSTRACT**

Disclosed are modified release oral tranexamic acid formulations and methods of treatment therewith.

57 Claims, 7 Drawing Sheets

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Product Information: Cyklokapron tablets (PfizerAu, approval 2001) with PI version pfpcyklt10308; PI Medsafe data sheet New Zealand 2008 (film coated tablet); and Pfizer data sheet (Spanish).
Product Information: Cyklonova 500mg film coated tablets; product Information date Oct. 5, 2007.
Product Information: Tranon 500mg film coated tablet, product information approved Apr. 16, 2008.
Product Information: Transamin Capsules, 250mg tablets, 500mg tablets, 50% powder, product information revision Jun. 2005.
Information Sheet: Transamin Otlo Pharmaceuticals, cap, tabs, injection.
Product Information: Transamin Capsures, dated Feb. 1998.
Information Sheet: Transamin Capsules, with Product Information: Transamin Tablets 500mg dated Feb. 1998.
Product Information: Cyklokapron Tablets 500 mg, product authorization Feb. 2005.
Product Information: Cyklokapron Tablets 500mg, film coat, product Jul. 31, 1968 with product information: cyklokapron 1000mg effervescent tablets, product authorization Dec. 7, 1995.
Product Information: Cycklo-f 500mg film coated tablet, authorization Jan. 31, 1997.
Product Information: Cyklokapron "Meda, Pfizer," injection, 500mg tablets, dated Oct. 24, 2006.
Product Information: Proklot film coated tablet, 500mg.
Product Information: Amchafibrin, 500mg.
Product Information: Tranexid, 250 mg capsules, 500mg membrane coated tablets.
Product Information: Tranfib, tablets and injection.
Product Information: Kalnex Capsules (250mg), tablets (500mg), injection, 1991.
Product Information: Hemostan 250, 500 mg capsules, injection.
Product Monograph: CykloKapron; Pfizer Canada Control No. 086534; Tranexamic acid tablets BP and Tranexamic acid injection BP date: Sep. 10, 2003, control No. 086534.
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Monograph: British Nat. Formulatry No. 43, 2002 sec. 2.11 Antifibrolytic drugs and haemostatics; Tranexamic acid pp. 123.
Information Sheet LExi-comp: Tranexamic Acid, Brand names.
Information Sheet Adam (internet) Tranexamic acid.
Monograph Health Canada; Cyklokapron; solution: for IV Use, date May 2005.
Product Information: Cyklokapron Injection, Ampoules 500mg per 5ml, Pharmacia Limited UK, authorization date Feb. 9, 1987.
Product Information: Cyklokapron tablets and Injection; 100mg/1ml water; Pharmacia & Upjohn revision Jun. 2008.
Product Information: Cyklokapron—tranexamic acid injection solution, 100mg/1ml. Pharmacia & Upjohn revision Jun. 2008.
Product Information: Cyklokapron—tranexamic acid injection solutions, 100mg/1ml. Pharmacia & Upjohn revision Jul. 2005, product registration, Jul. 31, 1968 (Dutch Language).
Product Information: Daiichi Pharmaceutical Co. Ltd., Transamin injection and Transamin S injection; 240mg/5ml, 250mg/2.5 ml and 1g/10ml.
CECMED Product Characteristics; ROTTAPHARMS S.L.; solution for Injection, IV, IV infusion, oral, 5mg/ml. vial.
Product Information: Dexa Medica, Traexid injection, injection 5% and injection 10%.
Product Information: Teva Pharmaceutical Industries Ltd., HEXAKAPRON; 500mg/5ml.
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Attorney Kevin W. McCabe; Notice Letter Regarding Paragraph IV Certification Against U.S. Patent No. 7,947,739 to Tranexamic Acid Formulations Pursuant to Section 505(j)(2)(B)(ii) of the Federal Food, Drug, and Cosmetic Act, dated May 27, 2011 (11 pages).
Janet Vaughn, Director, Regulatory Affairs, Watson Laboratories Florida, Notification of Certification of Invalidity and/or Noninfringement for U.S. Patent No. 7,947,739 Pursuant to Section 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act, dated May 24, 2011 (16 pages).

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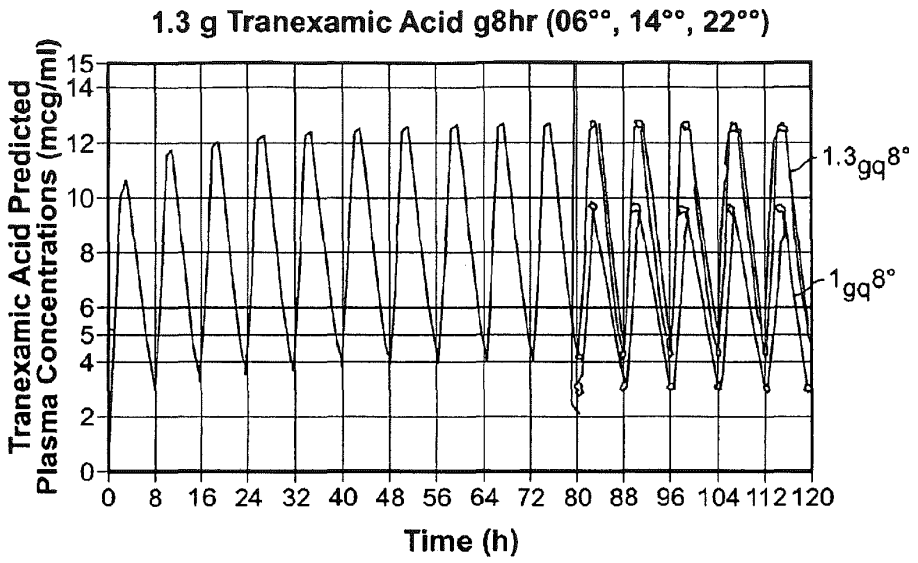
1.3 g Tranexamic Acid g8hr (06°°, 14°°, 22°°)
Tranexamic Acid Predicted Plasma Concentrations (mcg/ml)
0 2 4 5 6 8 10 12 14 15
0 8 16 24 32 40 48 56 64 72 80 88 96 104 112 120
Time (h)
1.3gq8°
1gq8°

FIG. 1

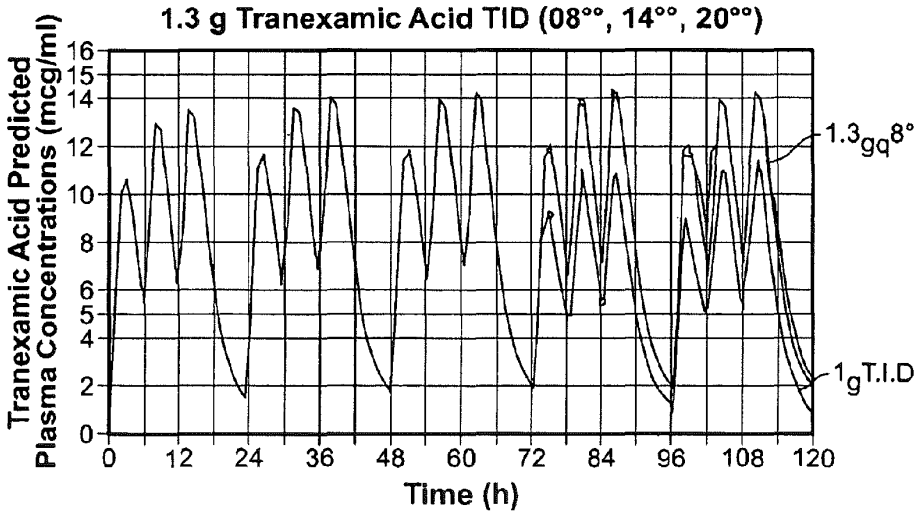
1.3 g Tranexamic Acid TID (08°°, 14°°, 20°°)
Tranexamic Acid Predicted Plasma Concentrations (mcg/ml)
0 2 4 5 6 8 10 12 14 15 16
0 12 24 36 48 60 72 84 96 108 120
Time (h)
1.3gq8°
1gT.I.D

FIG. 2

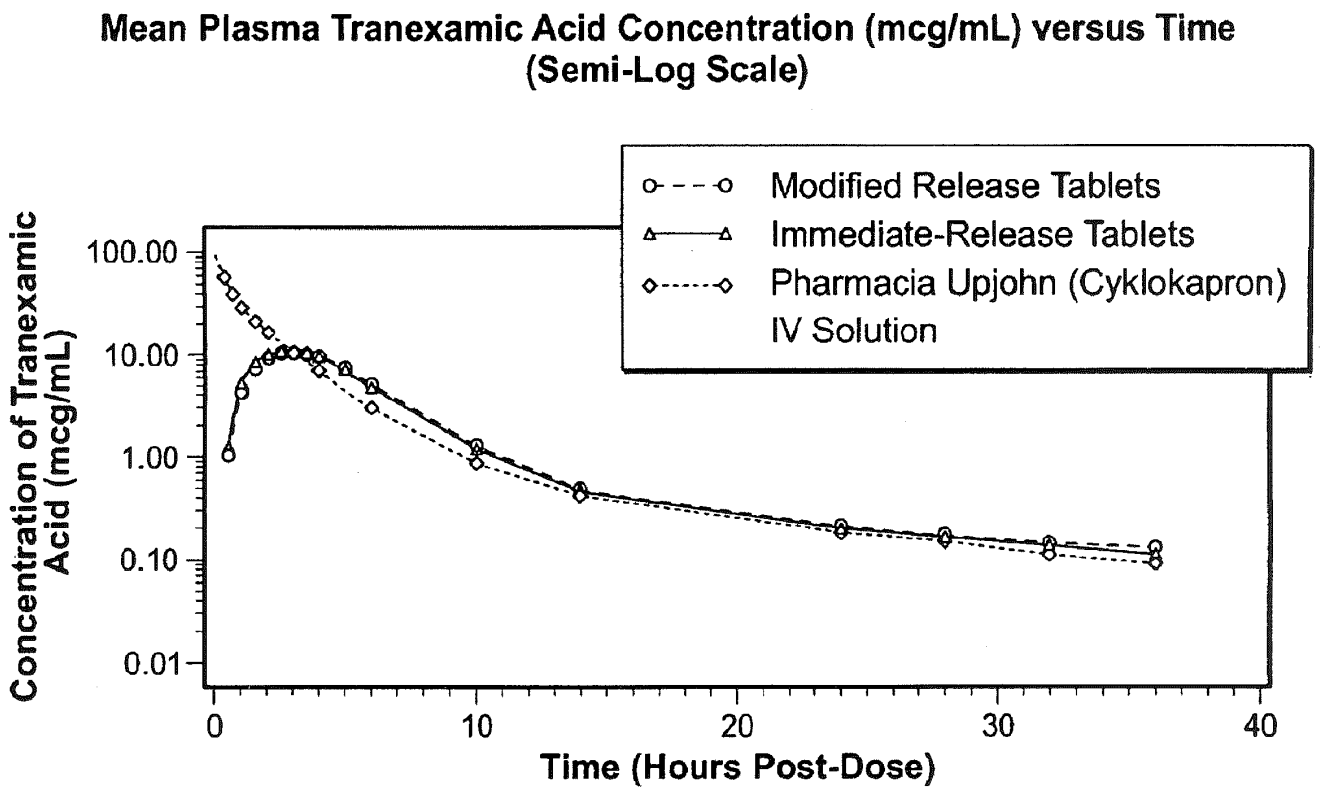

FIG. 3

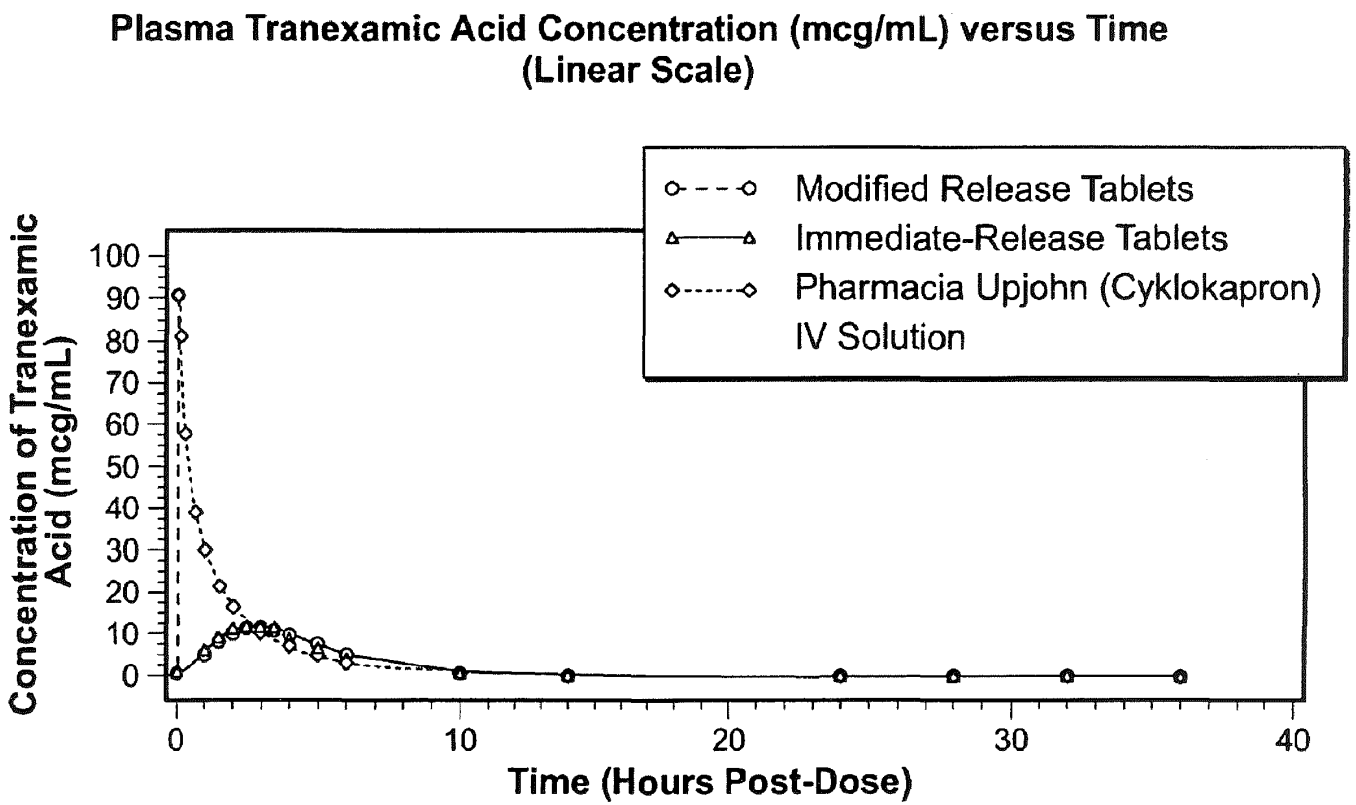

FIG. 4

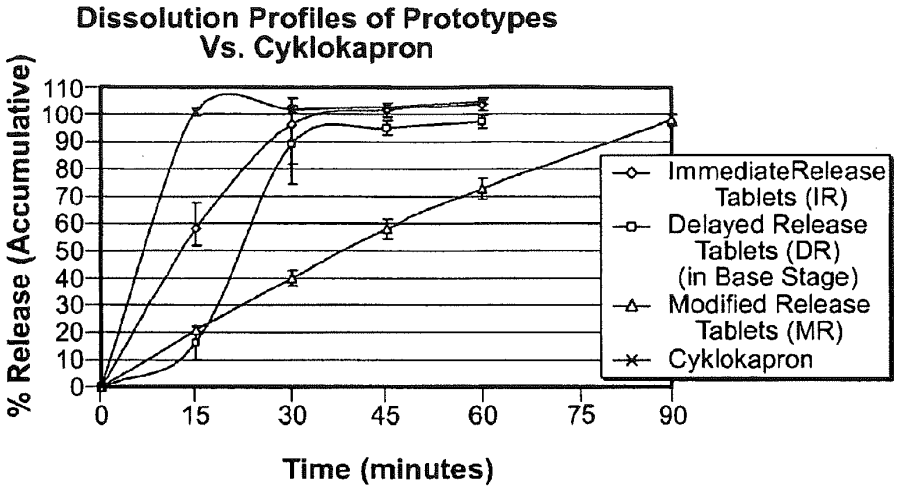
Dissolution Profiles of Prototypes
Vs. Cyklokapron
% Release (Accumulative)
110
100
90
80
70
60
50
40
30
20
10
0
0
15
30
45
60
75
90
Time (minutes)
ImmediateRelease Tablets (IR)
Delayed Release Tablets (DR) (in Base Stage)
Modified Release Tablets (MR)
Cyklokapron

FIG. 5

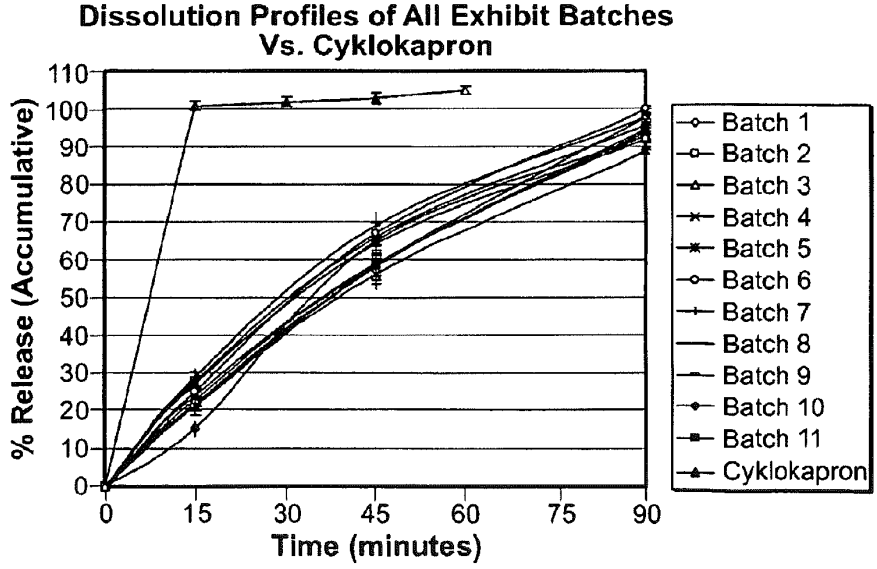
Dissolution Profiles of All Exhibit Batches
Vs. Cyklokapron
% Release (Accumulative)
110
100
90
80
70
60
50
40
30
20
10
0
0
15
30
45
60
75
90
Time (minutes)
Batch 1
Batch 2
Batch 3
Batch 4
Batch 5
Batch 6
Batch 7
Batch 8
Batch 9
Batch 10
Batch 11
Cyklokapron

FIG. 6

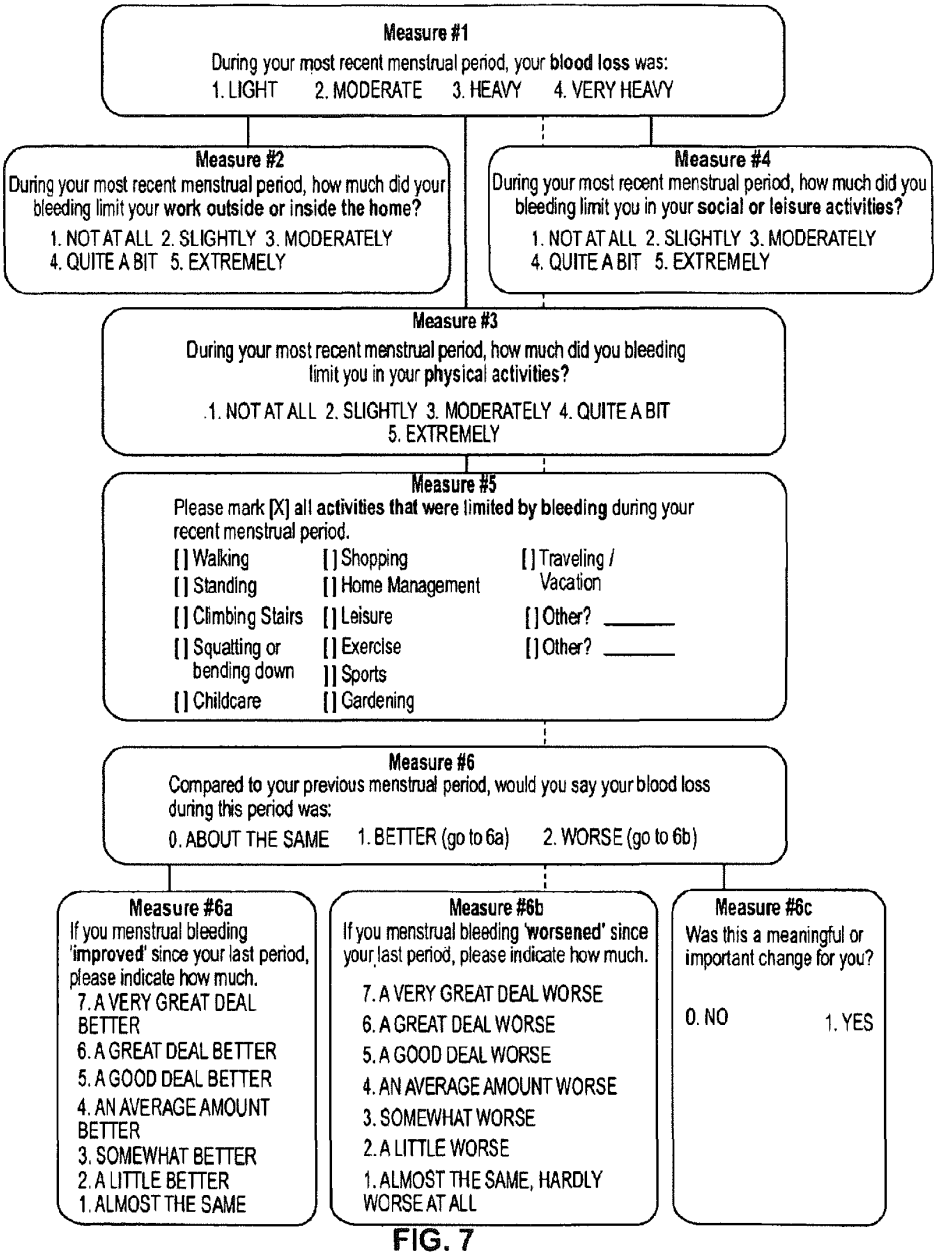
Measure #1
During your most recent menstrual period, your blood loss was:
1. LIGHT 2. MODERATE 3. HEAVY 4. VERY HEAVY
Measure #2
During your most recent menstrual period, how much did your bleeding limit your work outside or inside the home?
1. NOT AT ALL 2. SLIGHTLY 3. MODERATELY
4. QUITE A BIT 5. EXTREMELY
Measure #4
During your most recent menstrual period, how much did you bleeding limit you in your social or leisure activities?
1. NOT AT ALL 2. SLIGHTLY 3. MODERATELY
4. QUITE A BIT 5. EXTREMELY
Measure #3
During your most recent menstrual period, how much did you bleeding limit you in your physical activities?
.1. NOT AT ALL 2. SLIGHTLY 3. MODERATELY 4. QUITE A BIT
5. EXTREMELY
Measure #5
Please mark [X] all activities that were limited by bleeding during your recent menstrual period.
[ ] Walking
[ ] Standing
[ ] Climbing Stairs
[ ] Squatting or bending down
[ ] Childcare
[ ] Shopping
[ ] Home Management
[ ] Leisure
[ ] Exercise
]] Sports
[ ] Gardening
[ ] Traveling / Vacation
[ ] Other? _____
[ ] Other? _____
Measure #6
Compared to your previous menstrual period, would you say your blood loss during this period was:
0. ABOUT THE SAME 1. BETTER (go to 6a) 2. WORSE (go to 6b)
Measure #6a
If you menstrual bleeding 'improved' since your last period, please indicate how much.
7. A VERY GREAT DEAL BETTER
6. A GREAT DEAL BETTER
5. A GOOD DEAL BETTER
4. AN AVERAGE AMOUNT BETTER
3. SOMEWHAT BETTER
2. A LITTLE BETTER
1. ALMOST THE SAME
Measure #6b
If you menstrual bleeding 'worsened' since your last period, please indicate how much.
7. A VERY GREAT DEAL WORSE
6. A GREAT DEAL WORSE
5. A GOOD DEAL WORSE
4. AN AVERAGE AMOUNT WORSE
3. SOMEWHAT WORSE
2. A LITTLE WORSE
1. ALMOST THE SAME, HARDLY WORSE AT ALL
Measure #6c
Was this a meaningful or important change for you?
0. NO 1. YES

FIG. 7

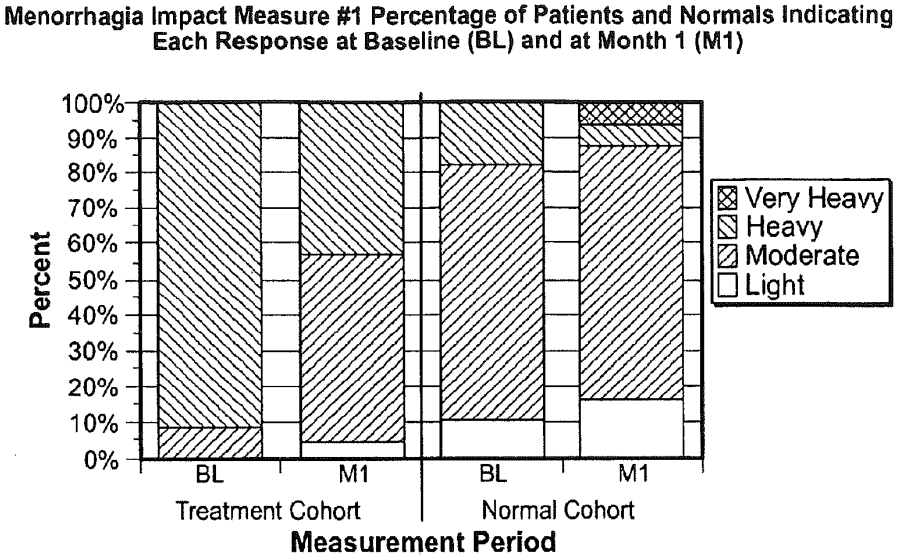
Menorrhagia Impact Measure #1 Percentage of Patients and Normals Indicating Each Response at Baseline (BL) and at Month 1 (M1)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percent
Very Heavy
Heavy
Moderate
Light
BL
M1
BL
M1
Treatment Cohort
Normal Cohort
Measurement Period

FIG. 8

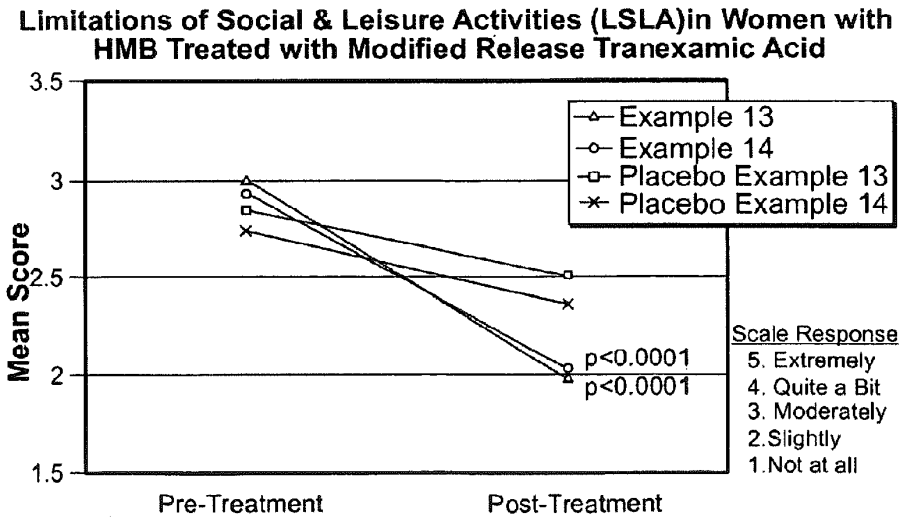
Limitations of Social & Leisure Activities (LSLA)in Women with HMB Treated with Modified Release Tranexamic Acid
3.5
3
2.5
2
1.5
Mean Score
Example 13
Example 14
Placebo Example 13
Placebo Example 14
p<0.0001
p<0.0001
Scale Response
5. Extremely
4. Quite a Bit
3. Moderately
2.Slightly
1.Not at all
Pre-Treatment
Post-Treatment

FIG. 9

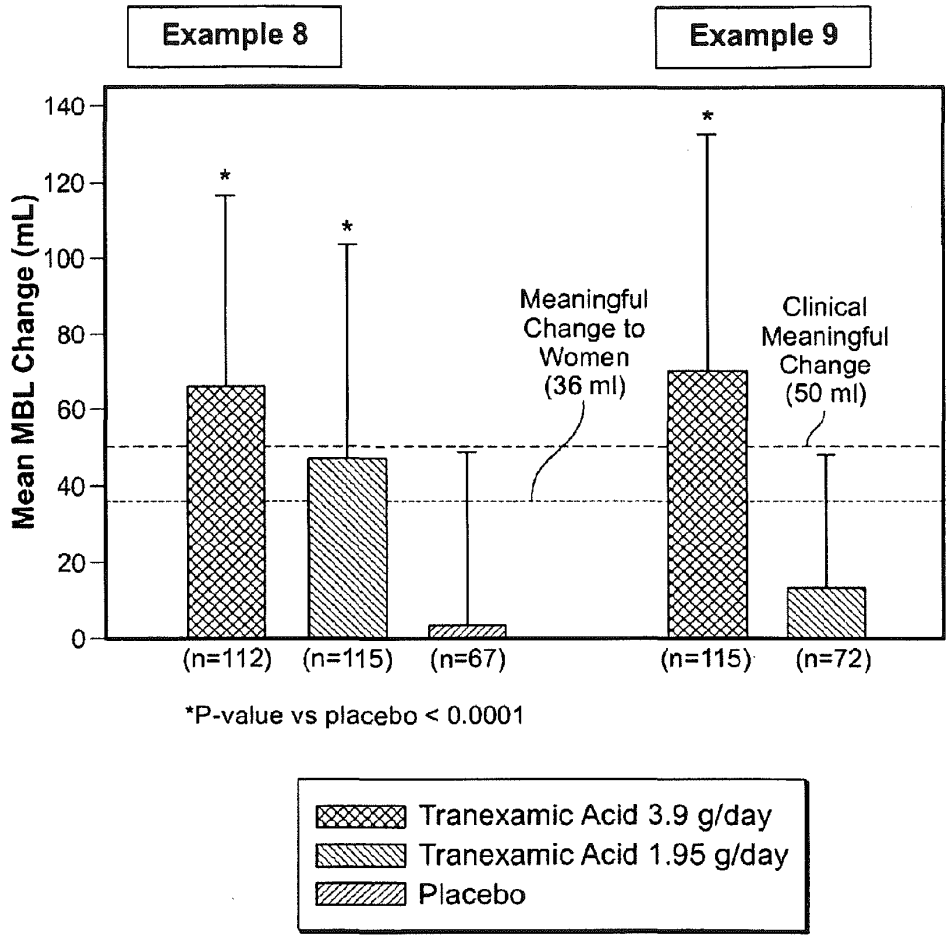
Example 8
Example 9
Mean MBL Change (mL)
140
120
100
80
60
40
20
0
*
*
*
Meaningful Change to Women (36 ml)
Clinical Meaningful Change (50 ml)
(n=112)
(n=115)
(n=67)
(n=115)
(n=72)
*P-value vs placebo < 0.0001
Tranexamic Acid 3.9 g/day
Tranexamic Acid 1.95 g/day
Placebo

FIG. 10

TRANEXAMIC ACID FORMULATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 12/228,489, which is a continuation of U.S. patent application Ser. No. 11/072,194 filed Mar. 4, 2005, now abandoned, which claims the benefit of U.S. Provisional Application No. 60/550,113, filed Mar. 4, 2004, and U.S. Provisional Application No. 60/592,885, filed Jul. 30, 2004, the disclosures of which are both hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

The invention is directed to modified release oral tranexamic acid formulations that preferably minimize or eliminate undesirable side effects and methods of treatment with these formulations.

BACKGROUND OF THE INVENTION

Tranexamic acid (trans-4-(aminomethyl)cyclohexanecarboxylic acid, Cyklokapron® (Pfizer) is an antifibrinolytic agent. That is, it helps to prevent lysis or dissolution of a fibrin clot which forms in the normal physiologic process of hemostasis. Its mechanism of action is as a competitive inhibitor of plasminogen activation, and as a noncompetitive inhibitor of plasmin; both plasminogen and plasmin are activators of fibrinolysis and active clot-lysing agents. Tranexamic acid thus helps to stabilize tibrin clots, which in turn maintains coagulation and helps to control bleeding.

Tranexamic acid is used to control excess bleeding, for example, excess bleeding that occurs during dental procedures in hemophiliacs and for heavy bleeding during menstruation (menorrhagia). Women suffering from menorrhagia are typically treated orally with 500 mg tranexamic acid tablets administered three or four times daily with a total daily dose ranging from 3 grams/day (two tablets every eight hours) to 6 grams/day (three tablets every six hours). However, this treatment may cause adverse gastrointestinal reactions, including nausea, vomiting, diarrhea, and cramping, etc. These gastrointestinal side effects are due to the quantity of tranexamic acid and/or rapid rate of release of tranexamic acid into the stomach with each dose, as well as the large quantity of excipients used in the tablet formulation that are introduced into the stomach. Such side effects, in addition to the cramping, bloating, pain, and other symptoms that may accompany menses, are undesirable, and a formulation of tranexamic acid is needed which will reduce or eliminate these side effects.

Menstrual Bleeding

Menstrual Bleeding disorders encompass a number of conditions including bleeding associated with uterine fibroids, endometriosis, or bleeding as a result of deficiencies in the clotting process for example, von-Willebrand's disease. Studies suggest that as many as 11% of the women who experience heavy menstrual bleeding, suffer from an inherited bleeding disorder such as von Willebrand's disease. Excessive Menstrual Bleeding is menstruation at relatively regular intervals but with excessive blood loss over the menses period which may be prolonged. Heavy Menstrual Bleeding (also referred to as "Menorrhagia") is a serious, persistent, and recurrent medical condition that is one of the most common complaints encountered by gynecologists and primary care physicians (Palep-Singh, 2007). A 2005 survey of 273 obstetrician/gynecologists found that they see an average of 18 to 25 symptomatic patients per month. Heavy Menstrual Bleeding is a hyperfibrinolytic condition defined as

cyclic, normal intervals of menstruation with excessive volume. Menorrhagia is often associated with a disruption in daily routines, work, and sexual activity leading to a significant decrease in health-related quality of life and time lost from work or school. While Menorrhagia is rarely life threatening, when undiagnosed and untreated, it may over time cause iron deficiency anemia and increased fatigue, both of which affect normal life activities, relationships, social activities, and various aspects of mental well-being (irritation, anxiety). Left untreated it may be associated with subsequent morbidity including dysmenorrhea, hospitalization, red blood cell transfusions and chronic pain. Annually, approximately 10% of women of reproductive age report Menorrhagia (Rees 1991; van Eijkeren, 1992) and according to the Center for Disease Control (CDC), 3 million women of reproductive age report Menorrhagia yearly, 60% of which have no known etiology. Studies report that as many as thirty percent of premenopausal women perceive their menses to be excessive.

Women suffering from menorrhagia often have greater uterine fibrinolytic activity than women with normal cyclic menstrual blood loss (MBL). High concentrations of plasminogen activators are found in both the uterus and menstrual fluid (Albrechtsen, 1956a,b). Rybo (1966) found significantly higher concentration of endometrial plasminogen activators in women with excessive menstrual bleeding compared to women with normal menstrual loss.

Causes of Menorrhagia include pelvic diseases (myomata [fibroids], adenomyosis or uterine polyps), intrauterine contraceptive devices, and systemic disorders (coagulopathies such as thrombocytopenia or von Willebrand's disease, and hypothyroidism). In contrast to menorrhagia, the term 'dysfunctional uterine bleeding' refers to excessive, prolonged or irregular bleeding from the endometrium that is unrelated to systemic disease (Wathen, 1995), and is usually associated with anovulation. Menorrhagia is also distinguished from other ovulatory bleeding disorders, such as metrorrhagia (intermenstrual bleeding), menometrorrhagia (irregular heavy menstrual bleeding) and polymenorrhea (menstrual cycle less than 21 days).

Diagnosis of Menstrual Blood Loss

In clinical trials, menstrual blood loss (MBL) is usually determined by measuring the amount of hemoglobin recovered from sanitary products during the menstrual cycle, using the alkaline hematin method (Fraser, 1994). However, it is important to remember that blood accounts for only about 50% of total menstrual flow, with endometrial transudate accounting for the remainder (Fraser, 1994). Total menstrual flow can be estimated by weighing of sanitary products or by comparisons with a pictorial blood loss assessment chart. However, the use of these quantitative and semi-quantitative methods is not practical in non-trial settings. Rather, the diagnosis of Menorrhagia in the healthcare clinic is made by medical providers on the basis of patient's perceived and self-reported medical history, routine laboratory assessments of the patient's general health status, and gynecological examinations.

Clinically heavy menstrual bleeding is sometimes defined as total blood loss exceeding about 80 ml per cycle or menses lasting longer than seven days. The volume lost however, varies widely. Clinically losses from about 30 ml to 60 ml, 60 to 80 ml, 80 to 100 ml, to as high as 1000 ml per cycle are observed. Menstrual blood losses of 50 to 60 ml are associated with a negative iron balance and iron deficiency anemia is diagnosed in about 67% of the women who lose an excess of 80 ml per day. Other criteria for diagnosing the condition include measuring the number and size of blood clots in the

meneges, or monitoring the use of pads or tampons. It is estimated that perhaps only ten percent of women who perceive their loss to be excessive actually fall within the clinical definition. The 80 ml definition has been repeatedly questioned, and alternative definitions broadened the blood loss range used for patient evaluations.

Blood loss volume assessments commonly require the collection and preservation of menstrual pads or tampons, the extraction of the pads and the accurate measurement of the blood content. Women are instructed to collect all sanitary towels and tampons during the course of the menstrual diagnosis period or the course of a clinical study period. Blood loss can be measured by extraction of the blood from the sanitary material with 5% sodium hydroxide followed with a spectrophotometric measurement of hematin at a wavelength of about 540 nm. The total blood loss can be calculated for an individual by comparison of the patients plasma blood hemoglobin measurement with the collected hemoglobin values.

The collection of the blood sample discourages the routine use of the test in the diagnosis or in the treatment of the condition. In the course of a routine visit with a physician other blood work may be appropriate but lacks a casual relation to the heavy bleeding disorder. The battery of routine laboratory tests may include patient blood hemoglobin, haematocrit, platelet count, bilirubin, serum creatinine and serum ferritin. In sum, diagnosis in the routine course of practice relies heavily on the woman's perception of the volume of blood lost during menses.

Diagnosis and Treatment of Heavy Menstrual Bleeding Disorders (Menorrhagia)

A number of medical and surgical interventions are available to treat menstrual bleeding disorders. Currently available non-surgical treatments for heavy bleeding disorders, include, hormonal treatments (e.g., oral contraceptives), high-dose progestin therapy, desmopressin acetate, ethamsylate, nonsteroidal anti-inflammatory drugs (NSAIDs), the antifibrinolytic drugs aminocaproic acid and tranexamic acid. Even with the drug treatments available, surgery remains a common treatment.

Although not approved for menorrhagia in the US, use of oral contraceptives for menorrhagia is widely accepted. Oral contraceptives may not be a preferred therapy for some women because of age (younger females), unwanted side effects (nausea and vomiting, breakthrough bleeding, weight change, migraines and depression), and safety concerns (increased risk of thromboembolism, stroke, myocardial infarction, hepatic neoplasia and gall bladder disease). High-dose progestin (synthetic versions of the hormone progesterone) may also be given to women with menorrhagia, either orally or by a progestin-releasing device inserted into the uterus (intrauterine device). Side effects include nausea, bloating, mood changes, and breast tenderness.

Although it is typically a last resort, desmopressin acetate is sometimes used to help lighten menstrual flow in women with menorrhagia. The effectiveness of desmopressin is thought to vary between individuals. Side effects include headache, tachycardia, facial flushing, and rare reports of thromboembolism.

NSAIDs are sometimes used to treat menorrhagia as they may reduce blood flow while providing analgesia for pain associated with the condition (Shaw, 1994). Side effects associated with chronic NSAID use include gastrointestinal bleeding, ulceration, and perforation; and renal effects such as hyperkalemia, hyponatremia, acute renal insufficiency, interstitial nephritis, and renal papillary necrosis.

Hysterectomy or endometrial resection are options if other forms of therapy are not effective or are unsuitable for some reason. Possible surgical complications include infection, uterine perforation, and other complications associated with major surgery.

Antifibrinolytic drugs, such as E-aminocaproic acid and tranexamic acid (immediate-release formulation) have been used to treat HMB in women with or without a diagnosed bleeding disorder (van Eijkeren, 1992; Bonnar, 1996; Vermylen, 1968; Nilsson, 1965). The available evidence from published literature suggests that tranexamic acid at doses of ~4 g/day (typically 1 g every 6 hours) is effective in the treatment of HMB and is associated with few side effects (Callender, 1970; Dunn, 1999; Edlund, 1995; Preston, 1995). In Sweden, the average dose of tranexamic acid to treat HMB is 3.9 g/day (Rybo, 1991). Thus, tranexamic acid is used extensively in Europe, Canada, Asia, Japan, Australia and New Zealand to treat menorrhagia, but is not approved for this indication in the US.

Tranexamic acid is a competitive inhibitor of plasminogen activation (see review by Dunn, 1999). Binding of tranexamic acid to plasminogen does not prevent conversion of plasminogen to plasmin by tissue plasminogen activator, but the resulting plasmin/tranexamic acid complex is unable to bind to fibrin. Thus, enzymatic breakdown of fibrin by plasmin (fibrinolysis) is inhibited. At higher concentrations, tranexamic acid is also a noncompetitive inhibitor of plasmin.

Before medical and surgical interventions can be initiated, diagnosis of a heavy menstrual bleeding disorder must be accomplished.

Diagnosis and treatment of disease often depends on the patient's perception and subsequent description of symptoms, the physician's evaluation of the patient's description, the physician observations of the patient and laboratory test results. Menstrual bleeding disorders do not lend themselves to physician observation or to routine laboratory testing. Patient observations and the physician's evaluation of the patient's description are subjective and thus variable. In addition a women's medical history has been found to be a poor predictor of menstrual blood loss. Neither the duration of menses nor the number of sanitary pads worn accurately corresponds to the woman's actual menstrual blood loss (Chimbira, Haynes, year). An objective assessment of blood loss using the alkaline haematin assay has been shown to be reproducible but it is not suited for routine clinical use by healthcare providers. To date no effective instrument for reliably diagnosing and/or monitoring the treatment of menstrual bleeding disorders has been developed despite the significant number of women who suffer from these conditions.

Previously, studies have focused on the impact of symptoms of bleeding disorders on patients' health related quality of life. As the effects of menstrual bleeding disorders are primarily symptomatic, the subjective outcome namely symptom alleviation, cannot be objectively measured. In research from European countries where the antifibrinolytic drug tranexamic acid is currently available, treatment with this antifibrinolytic has reduced heavy menstrual bleeding by 40-50% and improved the health-related quality of life of affected women on measures of social activity, work performance, productivity, cleanliness, overall functioning and tiredness.

Jenkinson et al, Quality in Health Care 1996; 5; 9-12 evaluated the validity and internal reliability of the short form-36 (SF36) health survey questionnaire in women presenting with menorrhagia. The study concluded that several questions on the questionnaire were difficult to answer for patients with heavy menstrual bleeding. Such problems were suggested as possible interferences with the validity of the measure. Jenkinson warns that because a subjective measure works well in

one population or with one group, this cannot be taken to imply its appropriateness for all groups or conditions.

Edlund, in an abstract from a seminar on Dysfunctional Uterine Bleeding, Feb. 23, 1994, indicates that a questionnaire was used in a Swedish study of 2205 women who described their menstruation as excessive.

Winkler in a study based in part on the Edlund work, concluded that the treatment of heavy menstrual bleeding with tranexamic acid increased the quality of life of the treated patients. The Winkler study was an open label uncontrolled usage study which included 849 patients. A questionnaire was used prior to treatment and after the first and third menstruation. The study indicates that 80% of the women were satisfied with the treatment. The questionnaire used a series of eight question combined with an assessment by the patients of the change in quantity of menstrual flow.

Ruta, D. A., Quality of Life Research, 4, (33-40), 1995 finds that menorrhagia is a common problem in gynecological practice and that women seek professional help primarily because of the deleterious effect on their quality of life. Ruta recognizing the importance of evaluating the effectiveness of the treatments developed a questionnaire based on the type of questions frequently asked when taking a gynecological history. A series of questions were devised which assessed fifteen factors including the duration of the period, the regularity of the period, pain, problems with soiling/staining, interference with work, interference with leisure. Ruta concluded that the clinical questionnaire may be useful in selecting patients for hysterectomy and assessing the outcome of conservative treatment especially in combination with the SF-36 questionnaire.

Diagnostic Test for Menstrual Bleeding

The alkaline haematine test described above provides quantitative assessments of the extent of menstrual bleeding. This test allows the physician to diagnose and monitor the progress of a women's menstrual process. However the test is impractical and difficult to perform. The test requires women to capture used menstrual pads over the course of her period, preserve the samples in a condition such that the blood content within the pad may be accurately extracted and quantitated. Requesting a patient to perform menses sample collection may be practical in the course of a clinical trial where procedures are specified and monitored however, in routine medical practice, the use of such a test procedure to diagnose and monitor, a women's menstrual bleeding is impractical and the data generated is unreliable.

The need remains to develop an assessment system which replaces previously studied diagnostic techniques and the alkaline haematine test and provides a reliable measure of both the occurrence of the disorder and the progress of the disorder. The present invention fills this need by providing a Heavy Menstrual Bleeding Instrument (HMBI) which is capable of diagnosing, and monitoring the treatment of a patient with a menstrual bleeding disorder.

There also remains a need to provide Heavy Menstrual Bleeding (HMB) therapy that is safe, efficacious and only administered during the monthly period of heavy menstruation, addresses the excessive fibrinolysis implicated in many causes of menorrhagia, and fills a currently recognized unmet medical need in the US. Therapy for HMB is expected to reduce the incidence and extent of iron-deficiency anemia, and to provide a nonhormonal medical therapy option in lieu of the numerous invasive procedures (e.g., transcervical endometrial resection) and major surgery (hysterectomy) performed annually.

SUMMARY OF THE INVENTION

Formulations of tranexamic acid which minimize or eliminate the undesirable gastrointestinal side effects in patients on oral tranexamic acid therapy, e.g. women treated for menorrhagia (heavy menstrual bleeding) are disclosed. The present invention is directed in part to a modified release formulation, formulated so that the release of tranexamic acid thereof from the dosage form occurs in a designed fashion to prevent a bolus of tranexamic acid being introduced into the stomach and available for dissolution in the gastric contents. Such modified release formulations reduce the concentration of tranexamic acid dissolved in the stomach contents such as e.g., preventing a large bolus of tranexamic acid being introduced in the stomach. The beneficial effect of this reduced tranexamic acid concentration is to lower the amount of tranexamic acid in the gastric contents so that there are fewer adverse effects with tranexamic acid therapy. This reduction in adverse effects preferably results in improved patient compliance with therapy, because preferably patients will not intentionally miss taking a dose to avoid these adverse side effects. Physicians will also preferably be more likely to initiate and maintain tranexamic acid treatment for their patients because of the reduced patient complaints.

It is an object of the invention to provide an oral dosage form comprising tranexamic acid which is suitable for administration on a two or three times a day basis to humans.

It is a further object of the invention to provide a modified release oral dosage form comprising tranexamic acid and a modified release material which provides for the modified release of the tranexamic acid and is suitable for administration on a two or three times a day basis.

It is a further object of certain embodiments of the present invention to provide a modified release oral dosage form comprising tranexamic acid and a modified release material which minimizes or eliminates the undesirable gastrointestinal side effects in patients on oral tranexamic acid therapy while maintaining or improving the therapeutic effect of tranexamic acid.

It is a further object of certain embodiments of the present invention to provide a method of treating a patient suffering from heavy menstrual bleeding (menorrhagia) by orally administering to the patient one or more dosage forms comprising tranexamic acid and a modified release material which provide(s) for therapeutically effective levels of tranexamic acid suitable for two or three times a day administration.

The above advantages and objects and others can be achieved by virtue of the present invention which is directed in part to a modified release oral dosage form comprising tranexamic acid or a pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis; said dosage form providing an in-vitro dissolution release rate of the tranexamic acid or pharmaceutically acceptable salt thereof, when measured by a USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C., of less than about 70% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes and about 100% by weight of said tranexamic acid or pharmaceutically acceptable salt thereof released by about 120 minutes.

In certain embodiments, the present invention is directed to a method of treating a patient in need of tranexamic acid or pharmaceutically acceptable salt thereof therapy comprising administering to the patient about 1300 mg of tranexamic acid or pharmaceutically acceptable salt thereof in at least one oral dosage form comprising said tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material

which provides a mean maximum plasma concentration (C_{max}) of tranexamic acid of from about 5 to about 17.5 mcg/ml, preferably from about 6.5 to about 15 mcg/ml, more preferably from about 9 to about 14.5 mcg/ml after single dose oral administration to humans.

In certain embodiments, the invention is further directed to a method of treating a patient in need of tranexamic acid or pharmaceutically acceptable salt thereof therapy comprising administering to the patient about 1300 mg of tranexamic acid or pharmaceutically acceptable salt thereof in at least one oral dosage form comprising said tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides a mean maximum plasma concentration (C_{max}) of tranexamic acid of from about 5 to about 25 mcg/ml, preferably from about 10 to about 20 mcg/ml, more preferably from about 12.5 to about 17.5 mcg/ml, most preferably about 15 to about 17 mcg/ml after steady state oral administration to humans.

In certain embodiments, the modified release oral dosage form of the present invention provides a mean T_{max} of tranexamic acid at from about 1 to about 5.5 hours, preferably at from about 2 to about 4 hours, more preferably at from about 2 to about 3.5 hours after oral administration of the dosage form to humans.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides a dissolution release rate in-vitro of the tranexamic acid or pharmaceutically acceptable salt thereof when measured by the USP 27 Apparatus Type II Paddle Method @50 RPM in 900 ml water at 37±0.5° C. of less than about 40% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, less than about 70% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, and not less than 50% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides a dissolution release rate in-vitro of the tranexamic acid or pharmaceutically acceptable salt thereof when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. of about 0% to about 40% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, from about 20% to about 60% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 30 minutes, from about 40% to about 65% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, from about 50% to about 90% by weight tranexamic acid or pharmaceutically acceptable salt thereof release at about 60 minutes, and not less than 60% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, which provides for a bioavailability of tranexamic acid of greater than 40%, from about 41% to about 60%, preferably from about 42% to about 50%, more preferably about 45% after oral administration to humans.

In certain embodiments, the present invention is further directed to a modified release oral dosage form comprising from about 585 to about 715 mg of tranexamic acid or pharmaceutically acceptable salt thereof, preferably about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof, and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis.

In certain embodiments, the present invention is directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis, the dosage form providing a reduction of at least one side effect selected from the group consisting of headache, nausea, vomiting, diarrhea, constipation, cramping, bloating, and combinations thereof, as compared to an equivalent amount of tranexamic acid or pharmaceutically acceptable salt thereof in an immediate release oral dosage fonn when administered across a patient population.

In certain embodiments, the present invention is directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release excipient, said dosage form providing for the release of the tranexamic acid or pharmaceutically acceptable salt thereof which is slower than an immediate release oral dosage form and faster than a controlled release oral dosage form, such that the modified release oral dosage form is suitable for administration two or three times a day.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, the dosage form being suitable for oral administration on a three times a day basis, and the dosage form providing a mean maximum plasma concentration (C_{max}) of tranexamic acid of from about 5 to about 17.5 mcg/ml, preferably from about 6.5 to about 15 mcg/ml, more preferably from about 9 to about 14.5 mcg/ml per 1300 mg tranexamic acid after single dose oral administration to humans.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, the dosage form being suitable for oral administration on a twice a day basis, and the dosage form providing a mean maximum plasma concentration (C_{max}) of tranexamic acid of from about 5 to about 40 mcg/ml, preferably from about 10 to about 30 mcg/ml per 1950 mg tranexamic acid after single dose oral administration to humans.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, the dosage form being suitable for oral administration on a three times a day basis, and the dosage form providing a mean plasma concentration of tranexamic acid of from about 5 to about 25 mcg/ml, preferably from about 7.5 to about 15 mcg/ml, more prefer-

ably from about 8 to about 10 mcg/ml, most preferably about 9 mcg/ml per 1300 mg tranexamic acid after steady state oral administration to humans.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, the dosage form being suitable for administration on a three times a day basis, and the dosage form providing a mean maximum plasma concentration (C_{max}) of tranexamic acid of from about 5 to about 25 mcg/ml, preferably from about 10 to about 20 mcg/ml, more preferably from about 12.5 to about 17.5 mcg/ml, most preferably about 15 to about 17 mcg/ml per 1300 mg tranexamic acid after steady state oral administration to humans.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and an modified release material, the dosage form being suitable for administration on a three times a day basis, and the dosage form providing a mean plasma trough concentration of tranexamic acid or pharmaceutically acceptable salt thereof of from about 2 to about 10 mcg/ml, preferably from about 3 to about 7.5 mcg/ml, more preferably about 4 to about 7 mcg/ml, most preferably about 5 to about 6 mcg/ml per 1300 mg tranexamic acid or after steady state oral administration to humans.

In certain embodiments, the invention is further directed to a method of treating a patient with a therapeutically effective amount of tranexamic acid or pharmaceutically acceptable salt thereof comprising administering to the patient two dosage forms of the present invention, each dosage form comprising from about 585 mg to about 715 mg of tranexamic acid or pharmaceutically acceptable salt thereof, preferably about 650 mg tranexamic acid or pharmaceutically acceptable salt thereof, and a modified release material such that the dosage form is suitable for oral administration on a three times a day basis.

In certain embodiments, the invention is further directed to a method of treating a patient with a therapeutically effective amount of tranexamic acid or pharmaceutically acceptable salt thereof comprising administering to the patient three dosage forms of the present invention, each dosage form comprising from about 585 mg to about 715 mg, preferably about 650 mg tranexamic acid or pharmaceutically acceptable salt thereof, and a modified release material such that the dosage form is suitable for oral administration on a twice a day basis.

In certain embodiments, the invention is directed to a dose of tranexamic acid or pharmaceutically acceptable salt thereof comprising two unit dosage forms of a modified release formulation, each unit dosage form of said modified release formulation comprising from about 585 mg to about 715 mg, preferably about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof, and a modified release material which provides for the release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dose provides a therapeutic effect when administered three times a day.

In certain embodiments, the invention is directed to a dose of tranexamic acid comprising three unit dosage forms of a modified release formulation, each unit dosage form of said modified release formulation comprising from about 585 mg to about 715 mg, preferably about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof, and a modified release material which provides for the release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dose provides a therapeutic effect when administered twice a day.

In certain preferred embodiments, the invention is further directed to a modified release oral dosage form including tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides a dissolution release rate in-vitro of the tranexamic acid or pharmaceutically acceptable salt thereof when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. of about 0% to about 40% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, from about 20% to about 60% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 30 minutes, from about 40% to about 80% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, from about 50% to about 95% by weight tranexamic acid or pharmaceutically acceptable salt thereof release at about 60 minutes, and not less than about 60% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes.

In certain preferred embodiments, the invention is further directed to a modified release oral dosage form including tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides a dissolution release rate in-vitro of the tranexamic acid or pharmaceutically acceptable salt thereof when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. of about 14% to about 22% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, from about 32% to about 50% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 30 minutes, from about 47% to about 71% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, from about 61% to about 92% by weight tranexamic acid or pharmaceutically acceptable salt thereof release at about 60 minutes, and from about 79% to about 100% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes.

In certain embodiments, the invention is directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and an effective amount of a modified release excipient such that the dosage form releases from about 10% to about 25% by weight tranexamic acid or pharmaceutically acceptable salt thereof every 15 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. In certain preferred embodiments, the dosage form releases about 18% to about 23% by weight tranexamic acid or pharmaceutically acceptable salt thereof every 15 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. Most preferably, the dosage form releases about 100% of said tranexamic acid or pharmaceutically acceptable salt thereof within about 120 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. In certain embodiments, the dosage form releases about 1% of said tranexamic acid or

pharmaceutically acceptable salt thereof every minute when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C.

In certain preferred embodiments, the modified release oral dosage form of the invention further provides a mean transit time of said tranexamic acid of 7.70±0.72 hours when administered across a patient population.

In certain preferred embodiments, the modified release oral dosage form of the invention further provides a mean absorption time of said tranexamic acid of 4.18±0.70 hours when administered across a patient population.

In certain further embodiments, the modified release oral dosage form of the present invention provides confidence intervals derived from In-transformed pharmacokinetic kinetic parameters AUC_{0-t}, AUC_{inf} and C_{max} for tranexamic acid in plasma which are within a 80-125% range of an immediate release formulation including an equivalent amount of tranexamic acid when administered across a patient population under fasted conditions.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides less than about 20 percent incidence of headache as a side effect after single dose oral administration across a patient population.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides less than about 10 percent incidence of nausea as a side effect when administered across a patient population, less than about 7 percent incidence of nausea when administered across a patient population, preferable less than about 5 percent incidence of nausea as a side effect when administered across a patient population, more preferably less than about 2 percent incidence of nausea as a side effect after single dose oral administration across a patient population.

In certain embodiments, the modified release oral dosage form of the present invention provides less CNS side effects (e.g., headache), less GI side effects (e.g., nausea), or combination thereof in comparision to an equivalent amount of tranexamic acid or pharmaceutically acceptable salt thereof in an immediate release formulation when administered across a patient population. Additionally or alternatively, in certain embodiments the dosage form provides less CNS side effects (e.g., headache), less GI side effects (e.g., nausea), or combination thereof in comparision to a therapeutically equivalent amount of tranexamic acid administered intravenously in five minutes or less across a patient population.

In certain embodiments, the modified release oral dosage form of the present invention provides for the reduction of at least one side effect as compared to an immediate release oral dosage form including an equivalent amount of tranexamic acid or pharmaceutically acceptable salt thereof, when the immediate release dosage form is administered across a same or different population of patients as said modified release dosage form, and wherein said immediate release dosage form releases all of said tranexamic acid or pharmaceutically acceptable salt thereof within about 45 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. Such side effects can be for example, headache, nausea, vomiting, diarrhea, constipation, cramping, bloating, and combinations thereof.

In certain embodiments, the modified release oral dosage form of the present invention provides a mean transit time of tranexamic acid which is at least about 20 minutes longer, preferably about 30 minutes longer, than an immediate release formulation including an equivalent amount of tranexamic acid when administered across a patient population.

In certain embodiments, the dosage form of the present invention provides a mean absorption time of tranexamic acid which is at least about 20 minutes longer, preferably about 30 minutes longer, than an immediate release formulation including an equivalent amount of tranexamic acid when administered across a patient population.

In certain preferred embodiments, the therapeutically effective dose of the tranexamic acid or pharmaceutically acceptable salt thereof is provided via the administration of two or more dosage units. For example, if the dosage unit comprises 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and the dose for administration is about 1300 mg then two dosage units would be administered to a patient in need of such treatment, or for example, when the dose for administration is 1950 mg, three dosage units would be administered.

In certain preferred embodiments, the invention is further directed to a method of treating a patient with one or more modified release oral dosage forms comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, wherein the oral dosage form provides a therapeutically effective plasma level of tranexainic acid or pharmaceutically acceptable salt thereof in accordance with a three times a day (TID) dosing schedule, and the therapeutically effective dose administered comprises about 1300 mg of tranexamic acid or pharmaceutically acceptable salt thereof.

In certain preferred embodiments, the invention is further directed to a method of treating a patient with one or more modified release oral dosage forms comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, wherein the oral dosage form provides a therapeutically effective plasma level of tranexamic acid or pharmaceutically acceptable salt thereof in accordance with a twice a day (BID) dosing schedule, and the therapeutically effective dose administered comprises about 1950 mg of tranexamic acid or pharmaceutically acceptable salt thereof.

In certain embodiments, the invention is directed to a method of providing a tranexamic acid plasma concentration within the range of about 5 mcg/mL to about 15 mcg/mL by administration of a modified release formulation of the present invention comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material on a three times a day basis to a patient in need of tranexamic acid or pharmaceutically acceptable salt thereof treatment.

In certain embodiments, the invention is further directed to a method of treating a human patient with heavy menstrual bleeding (e.g., menorrhagia) comprising administering about 1300 mg of tranexamic acid or pharmaceutically acceptable salt thereof on a three times a day basis to the human patient to provide a tranexamic acid or pharmaceutically acceptable salt thereof plasma concentration within the range of about 5 mcg/mL to about 15 mcg/mL after steady state oral administration to a human patient.

In certain embodiments, the invention is directed to a method of treating a patient suffering from menorrhagia, including patients with heavy menstrual bleeding due to

fibroids, conization of the cervix, epistaxis, hyphema, hereditary angioneurotic edema, a patient with a blood coagulation disorder undergoing dental surgery, combinations thereof, and the like, by administering at least one dosage form of the present invention to the patient in need in tranexamic acid or pharmaceutically acceptable salt thereof therapy.

In certain embodiments, the invention is directed to a method of treating heavy menstrual bleeding with a therapeutically effective dose of at least one oral formulation of the present invention comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material wherein the menstrual blood loss per menstrual cycle is reduced by at least about 10 ml, preferably at least about 20 ml, more preferably at least about 40 ml. In a most preferred embodiment the menstrual blood loss per menstrual cycle is reduced by greater than or equal to about 50 ml.

In certain embodiments, the invention is directed to a method of treating heavy menstrual bleeding with a therapeutically effective dose of at least one oral formulation of the present invention comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which upon oral administration to a human female reduces the blood loss per menstrual cycle by about 35 ml to about 200 ml, preferably about 40 ml to about 175 ml, more preferably from about 50 ml to about 150 ml.

In certain embodiments, the invention is further directed to a method of treating heavy menstrual bleeding with a therapeutically effective dose of at least one oral formulation of the present invention comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which upon oral administration to a human female reduces the blood loss per menstrual cycle by about 20% to 100%, preferably from about 20% to about 70%.

In certain other embodiments, the present invention is directed to the use of the tranexamic acid formulations described herein for the treatment of heavy menstrual bleeding (menorrhagia) and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure, and physical activities.

The menstrual blood loss can be measured by procedures known in the art. For example, in certain embodiments, the menstrual blood loss can be determined by a procedure described by (i) L. Hallbert, et al. in "Determination of Menstrual Blood Loss", *Scandinav. J. Clin. & Lab. Investigation,* 244-248, 16, 1964, wherein the procedure is performed by extracting the menstrual blood from vaginal tampons and towels with a sodium hydroxide solution, converting heme chromogens to alkaline hematin, which is determined spectrophotometrically; or (ii) the menstrual blood loss can be determined by a procedure described by J. Newton, M. D., et al., in "A Rapid Method for Measuring Menstrual Blood Loss Using Automatic Extraction.", *Contraception,* 269-282, September 1977, Vol. 16, No. 3, wherein the procedure is based upon the formation of alkaline haematin after the blood has been extracted from vaginal tampons and sanitary towels by an automatic Stomacher Lab-Blender. The disclosures of the aforementioned articles are hereby incorporated by reference in their entireties.

In certain embodiments, the modified release material may be incorporated in a coating applied onto e.g., a tablet comprising the tranexamic acid or pharmaceutically acceptable salt thereof, or may be incorporated into a matrix with the tranexamic acid or pharmaceutically acceptable salt thereof, or a combination thereof. For example, in certain preferred embodiments, the modified release material is a controlled release material such as a gel-forming or hydratable polymer which is added to e.g., a matrix composition comprising the tranexamic acid or pharmaceutically acceptable salt thereof.

In certain embodiments, the tranexamic acid for use in the methods and formulations of the present invention is in the form of a pharmaceutically acceptable salt thereof. Such salt forms include for example and without limitation the sodium salt, potassium salt, calcium salt, magnesium salt and the like; as well as the hydrochloride, hydrobromide, sulfate, phosphate, formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate-methanesulfonate salt forms, and the like. Preferably the active ingredient for use in accordance with the present invention is tranexamic acid.

An "immediate release oral dosage form" for purposes of the present invention is a dosage form which releases all of active ingredient (e.g., tranexamic acid) included therein within about 45 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C.

A "modified release oral dosage form" for purposes of the present invention is an oral dosage form which releases the active ingredient (e.g., tranexamic acid) included therein in a manner that is slower than an immediate release oral dosage form and faster than a controlled release oral dosage form, when the dosage forms include the same amount of active as the modified release oral dosage form. One definition of the terms "slower" and "faster" as used in this application is that they are meant to represent a statistically significant difference at each measured 15 minute interval after the start of in-vitro dissolution. In certain preferred embodiments, the modified release oral dosage form of the present invention provides an in-vitro dissolution release rate of tranexamic acid or pharmaceutically acceptable salt thereof, when measured by a USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C., of less than about 70% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes and about 100% by weight of said tranexamic acid or pharmaceutically acceptable salt thereof released by about 120 minutes.

A "controlled release oral dosage form" for purposes of the present invention is a dosage form which releases all of the active ingredient (e.g., tranexamic acid) included therein after about 4 hours or more when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C.

The term "C_{max}" unless otherwise indicated is meant for purposes of the present invention to mean the maximum plasma concentration of a medicament achieved after single dose administration of a dosage form, or the maximum plasma concentration of a medicament achieved over a dosing interval from multiple-doses at steady-state in accordance with the present invention.

The term "T_{max}" is meant for purposes of the present invention to mean the elapsed time from administration of a dosage form to the time the C_{max} of the medicament is achieved.

The term "steady state" means that the amount of the drug reaching the system is approximately the same as the amount of the drug leaving the system. Thus, at "steady-state", the patient's body eliminates the drug at approximately the same rate that the drug becomes available to the patient's system through absorption into the blood stream.

The term "mean" for purposes of the present invention, when used to define a pharmacokinetic value (e.g., T_{max}), unless specified otherwise, represents the arithmetic mean value measured across a patient or subject population.

The term "three times a day (TID) basis" for purposes of the present invention, means that the dosage regimen is to be administered three times a day, preferably on a schedule of every 8 hours.

The term "mean transit time" is understood by those skilled in the art and means the time-point where 63.2% of the total AUC is attained after oral administration, or 63.2% of the IV dose is eliminated, as described in *Applied Pharmacokinetics, Principles of Therapeutic Drug Monitoring*, Second Edition (1986), edited by William E. Evans, et al., the disclosure of which is hereby incorporated by reference in its entirety.

The term "mean absorption time" is understood by those skilled in the art and means a quantitative parameter which summarizes how long, on average, the drug molecule remains unabsorbed, i.e. persists in its dosage form and in the gastrointestinal tract, also as described in *Applied Pharmacokinetics, Principles of Therapeutic Drug Monitoring*, Second Edition (1986), edited by William E. Evans, et al. Unlike the absorption rate constants (ka) which can be skewed, the mean absorption timeis not affected by incomplete release of drug from its dosage form, irregular absorption, lag-time, mixed zero-order dissolution rates, changing GI motility, GI blood flow, first-pass effect, etc.

"Therapy" for excessive menstrual bleeding is defined for the purpose of this invention as one or more courses of treatment with an antifibrinolytic agent such as, but not limited to, tranexamic acid, aminocaproic acid, and any pharmaceutically acceptable salts, esters, derivatives, pro-drugs, metabolites, and analogues of any of the foregoing antifibrinolytic agents.

The term "heavy menstrual bleeding" is defined for purposes of the present invention as a perceived blood loss of at least heavy to very heavy which may correspond to a periodic blood loss of at least about 30 ml per cycle to as much as 1000 ml per cycle as measured by the alkaline hematin test. The periodic blood loss perceived or as measured with the alkaline hematin test may vary depending on the severity of the condition and the physiological make up of the individual patient. Therefore, heavy menstrual bleeding may include periodic blood losses of at least about 30 ml per cycle. Losses from between about 30 ml, about 40 ml, about 50 ml, about 60 ml, about 70 ml, about 80 ml, about 90 ml to about 300 ml are contemplated as are losses greater than 300 ml, such as for example, losses between about 300 ml to about 1000 ml.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** depicts concentration-time profiles for simulated administration of the 1.3 g tranexamic acid modified release formulation of Example 1 at a Q8H (every 8 hours) dosing schedule of 6:00 AM, 2:00 PM, 10:00 PM comparing it with 1 g administered Q8H.

FIG. **2** depicts concentration-time profiles for simulated administration of the 1.3 g tranexamic acid modified release formulation of Example 1 at a TID (three times a day) dosing schedule of 8:00 AM, 2:00 PM, 8:00 PM comparing it with 1 g administered TID.

FIG. **3** depicts mean plasma concentration-time profiles on a semi-log scale over 36 hours for the study of Example 4.

FIG. **4** depicts mean plasma concentration-time profiles on a linear scale over 36 hours for the study of Example 4.

FIG. **5** depicts the dissolution profiles of the modified release tranexamic acid formulation of Example 1; the immediate release tranexamic acid formulation of Example 2; the delayed release tranexamic acid formulation of Example 3A, and the commercial Cyklokapron immediate release formulation of Example 4A.

FIG. **6** depicts the dissolution profile of all of the exhibit batches (Table 10A) of the modified release tranexamic acid formulations of the present invention and the commercial Cyklokapron immediate release formulation of Example 4A.

FIG. **7** is a listing of the Menorrhagia Impact Measures of the present invention.

FIG. **8** is a graph of Menorrhagia Instrument measure #1 percentage of patients and normals indicating each response at baseline (BL) and at one (1) month (M1) of Example 7.

FIG. **9** is a graph of the limitations of social and leisure activities (LSLA) in women with Heavy Menstrual Bleeding (HMB) in accordance with the treatment regimens administered in Examples 8 and 9.

FIG. **10** is a graph of the mean menstrual blood loss change from the clinical studies of Examples 8 and 9.

DETAILED DESCRIPTION

The tranexamic acid (API) utilized in the formulations of the present invention is available from various manufacturers. The tranexamic acid particles utilized in the present invention may range from about 0.1 to about 550 microns. For example, the tranexamic acid particles may have a particle size range from <about 0.5 to about 520 microns.

The tranexamic acid particles utilized in the present invention may have a D_{25} particle size distribution ranging from about 5 to about 15 microns, a D_{50} particle size distribution ranging from about 14 to about 73 microns, and a D_{75} particle size distribution ranging from about 30 to about 205 microns.

The particle size of the tranexamic acid utilized may also have a particle size range wherein about 1% of the particles are of a size greater than about 250 microns, about 8% of the particles are of a size of about 180 microns, about 9% of the particles are of a size of about 150 microns, about 4% of the particles are of a size of about 125 microns, about 20% of the particles are of a size of about 75 microns, about 14% of the particles are of a particle size of about 45 microns, and about 44% of the particles are of a particle size less than about 45 microns.

The tranexamic acid utilized may also have a particle size range wherein about 5% of the particles are of a size greater than about 250 microns, about 12% of the particles are of a size of about 180 microns, about 14% of the particles are of a size of about 150 microns, about 14% of the particles are of a size of about 125 microns, about 29% of the particles are of a size of about 75 microns, about 12% of the particles are of a particle size of about 45 microns, and about 14% of the particles are of a particle size less than about 45 microns.

The tranexamic acid utilized may also have a particle size range wherein about 2% of the particles are of a size greater than about 250 microns, about 7% of the particles are of a size of about 180 microns, about 9% of the particles are of a size of about 150 microns, about 4% of the particles are of a size of about 125 microns, about 20.5% of the particles are of a size of about 75 microns, about 16% of the particles are of a particle size of about 45 microns, and about 41.5% of the particles are of a particle size less than about 45 microns.

The tranexamic acid utilized may also have a particle size range wherein about 0% of the particles are of a size greater than about 250 microns, about 5% of the particles are of a size of about 180 microns, about 12% of the particles are of a size of about 150 microns, about 11% of the particles are of a size of about 125 microns, about 31% of the particles are of a size of about 75 microns, about 17% of the particles are of a particle size of about 45 microns, and about 24% of the particles are of a particle size less than about 45 microns.

The tranexamic acid utilized may also have a particle size range wherein about 20% of the particles are of a size of about 125 microns, about 20% of the particles are of a size of about 75 microns, about 20% of the particles are of a particle size of about 45 microns, and about 45% of the particles are of a particle size less than about 45 microns.

The dosage regimen typically listed for tranexamic acid in HMB (Heavy Menstrual Bleeding) therapy is 1-1.5 g per dose administered three-four times a day at the onset of copious menstrual bleeding and continued for the first 3-5 days of the menstrual cycle. However, the most frequently reported dosage regimen of tranexamic acid is an immediate release oral formulation in which 1 g tranexamic acid is administered four times a day (4 g per day) for HMB therapy outside of the US. Knowledge of this common regimen is supported by a careful review of the randomized controlled trials published in the medical literature, product labeling from other countries' regulatory authorities having the product approved for HMB therapy, utilization data from Sweden (Rybo 1991), correspondence and interviews with non-US clinicians having experience with the product. That regimen is currently the dosage being studied by the US Center for Disease Control (CDC) in women with HMB associated with bleeding disorders.

The absolute bioavailability of tranexamic acid observed when administering the European commercial formulation (Cyklokapron, Kabi AB, Sweden Batch 90288; assay 499 mgm/tablet) to male subjects is approximately 35% and its elimination correlates with renal creatinine clearance. Peak serum tranexamic acid concentrations occur approximately 3 hours after the oral administration of a European immediate-release tablet formulation (>85% dissolved at 15 minutes) (Pilbrant, et al., *Eur. J. Clin. Pharmacol*, (1981)-20:65-72). By comparison, the in vivo absorption profile observed with the European immediate-release formulation is slow and very gradual over 3 hours. Specifically, tranexamic acid serum concentrations are 9, 41, 73, 88 percent (with food), and 22, 63, 85, and 98 percent (fasting) of maximal absorption at 0.5, 1, 1.5 and 2 hours after a 2 g oral dose, respectively. Although not wishing to be held to any specific theory, it is presently hypothesized that tranexamic acid oral absorption appears to be controlled by a non-dissolution rate limited process, i.e. the rate and extent of oral absorption is a function of a transmembrane passage-limited process, in order to explain the disparity between the time of product dissolution and relatively prolonged tmax (time to achieve the peak serum concentration).

Preferably, the goal of the formulation, dose strength and dosage regimen of the invention, is to provide HMB therapy which achieves from about 20% to 100% reduction in menstrual blood loss per menstrual cycle. In accordance with certain embodiments of the present invention, the preferred tranexamic acid dose of 1.3 g every 8 hours is predicted to provide an average serum tranexamic acid concentration comparable to that produced by a 1 g every 6 hour regimen (i.e. 12.4 mcg/mL), with associated peaks and troughs falling approximately within the therapeutic antifibrinolytic range (5-15 mcg/mL; Cyklokapron NDA 19-280). In certain embodiments, a two-compartment oral absorption and elimination simulation model coupled with pharmacokinetic data (Pilbrant, et al., *Eur. J. Clin. Pharmacol*, (1981)-20:65-72), and modified-release tablet dissolution performance information were used to determine the preferred lead dosage regimen.

In immediate release formulations the entire dose and the soluble components in the dosage form dissolve in gastrointestinal fluid and present a high concentration of solutes for absorption. The most frequently reported adverse effects are primarily confined to the proximal gastrointestinal tract (nausea and vomiting). These adverse symptoms appear to be related to the drug load presented to the gastric mucosa, since this effect can be minimized by reducing the immediate-release oral formulation dose or administering the product slowly by the intravenous route. In certain embodiments, a lower incidence of proximal gastrointestinal adverse effects is obtained with the preferred oral modified release formulation (e.g., dosed 1.3 g every 8 hours) of the invention, e.g., because of the modified release properties of the drug product formulation.

In certain embodiments, the oral dosage form of the present invention provides for an increased bioavailability as compared to immediate release oral dosage forms currently available (e.g., Cyclokapron). In certain preferred embodiments the increased bioavailability allows therapeutic plasma levels of tranexamic acid to be reached with a lower dose of drug. Preferably, the increased bioavailability also decreases the amount of tranexamic acid that remains unabsorbed in the gastrointestinal which leads to decreased incidence of side effects that are typically associated with formulations that provide higher levels of unabsorbed tranexamic acid and prolonged exposure of the gastrointestinal tract to the higher tranexamic acid levels. Preferably the oral dosage form of the present invention provides for a bioavailability of tranexamic acid of greater than 40%, from about 41% to about 60%, preferably from about 42% to about 50%, more preferably about 45% after oral administration to humans.

The modified release oral formulations of tranexamic acid of the present invention provides a release of the drug which is slower than that of the immediate release 500 mg Cyklokapron product current marketed in Canada which provided a mean release rate of 100% by weight tranexamic acid released by about 15 minutes when measured utilizing USP 27 Apparatus Type II paddle method @ 50 RPM in 900 ml water at 37±0.5° C.

In certain embodiments, the modified release oral formulations may be described as providing a mean transit time through the proximal gastrointestinal mucosa which takes approximately one half hour longer than an immediate release formulation. In other preferred embodiments, the modified release formulations of the invention provide a rate of release of (dissolved) tranexamic acid from the dosage form in-vitro which is approximately 20, 40, 60, 80, and 100 percent of the total dose at 0.25, 0.5, 0.75, 1 and 1.5 hours, respectively. In certain preferred embodiments, such a release rate in-vitro demonstrates that the formulations of the present invention provide a relative reduction in the amount and rate of dissolved tranexamic acid presented to the proximal gastric mucosa to approximate 20, 40, 60, 80, and 100 percent of the total dose at 0.25, 0.5, 0.75, 1 and 1.5 hours, respectively, after oral administration.

In certain embodiments, the majority of tranexamic acid absorption appears to occur slowly distal to the stomach, and assuming linear pharmacokinetics, the modified release formulation produces an absorption profile which is comparable to that achieved with the currently available oral immediate release formulations used outside the U.S.

In accordance with the present invention a modified release tranexamic acid tablet for oral administration is disclosed. Preferably, the tablet contains at least one material (defined herein as any substance other than the active, i.e., tranexamic acid) which minimizes or eliminates the adverse gastrointestinal side effects in patients, for example, women dosed with oral tranexamic acid for treatment of menorrhagia.

The modified release oral dosage forms of tranexamic acid for purposes of the present invention include formulation ingredients and/or configurations which are typically utilized for formulations known in the art as extended, sustained and controlled release formulations, although modified to provide a desirable release rate in keeping with the teachings of the present invention. The modified release formulations preferably decrease the concentration of tranexamic acid and materials dissolved in the stomach fluids after dosing by controllably releasing tranexamic acid over a period of time, as opposed to immediate release formulations which release the entire dose of tranexamic acid all at once. The modified release formulations of the present invention thus minimize or prevent gastrointestinal reactions and side effects that occur when a dose of tranexamic acid is ingested and immediately reaches the stomach.

The modified release dosage forms of the present invention may be prepared as; tablets, capsules, granules, pellets, powders, dragees, troches, non-pariels, pills or encapsulated suspension, and may be packaged into capsules, sachets, etc. Such dosage forms may be prepared by any formulation technique where release of the active substance (tranexamic acid) from the dosage form is modified to occur at a slower rate than from an immediate release product. In these formulations, tranexamic acid release occurs in the stomach and/or intestine, but at a slower rate so that a bolus of dissolved drug does not reach the lining of the stomach and cause adverse effects, or adverse effects occur with a lower intensity or frequency because of the lower concentration of tranexamic acid. Hence, adverse effects are preferably reduced, minimized or eliminated.

Methods of preparing modified release formulations are found in Modified Release Drug Delivery Technology, Rathbone, Hadgraft, and Roberts, Eds., Drugs and the Pharmaceutical Sciences, Vol. 126, Marcel Dekker Inc., New York, 2003; Modern Pharmaceutics, Third Edition, Banker and Rhodes, Eds. Drugs and the Pharmaceutical Sciences, Vol. 72, Marcel Dekker Inc., New York, 1996; Sustained and Controlled Release Drug Delivery Systems, Robinson, Ed., Drugs and the Pharmaceutical Sciences, Vol. 6, Marcel Dekker Inc., NY 1978; Sustained Release Medications, Chemical Technology Review No. 177, Johnson, Ed., Noyes Data Corporation 1980; Controlled Drug Delivery, Fundamentals and Applications, Second Edition, Robinson and Lee, Eds., Marcel Dekker Inc., New York, 1987, and as described in U.S. Pat. No. 6,548,084, each of these references being expressly incorporated by reference herein in its entirety.

Preferably, a modified release form, makes tranexamic acid available over an extended period of time after ingestion. Modified release dosage forms coupled with the digestion process and the absorption process in the gastrointestinal tract cause a reduction in the amount of tranexamic acid in solution in the gastrointestinal tract compared to dosing tranexamic acid presented as a conventional dosage form (e.g., as a solution, or as an immediate release dosage form). The modified release formulation may be verified by in vitro dissolution testing and in vivo bioequivalence documentation, according to Food and Drug Administration standards, e.g., as set forth at www.fda.gov, 21 CFR §314, 320, and also at USP 23 NF 18 §711, 724. For example, an in vitro dissolution test such as USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. may be used to verify the release of the tranexamic acid from the dosage form.

Tranexamic acid modified release tablets may be formulated to provide a dose of tranexamic acid, typically about 500 mg to about 2 grams from one to two tablets, within about the first one to two hours after the tablet is ingested. Thus, tranexamic acid release occurs at a designed rate over a period e.g., about 60 minutes to about 120 minutes. The rate of tranexamic acid release over this period of time is designed to provide a reduced concentration of tranexamic acid in the stomach while allowing the absorption of tranexamic acid to occur throughout the gastrointestinal tract. Absorption of tranexamic acid typically begins as soon as tranexamic acid is released from the dosage form and is dissolved in the gastrointestinal fluids contacting the membranes which line the gastrointestinal tract. The rate of release of tranexamic acid from the dosage form and the absorption of drug by the gastrointestinal mucosa help to maintain low concentrations of drug in the gastrointestinal fluids. The lowered concentrations preferably result in lower intensity, frequency, and/or severity of gastrointestinal adverse side effects. The designed rate of release of tranexamic acid from the dosage form in the stomach and the upper small intestine, the natural emptying of gastric juice containing any dissolved tranexamic acid from the stomach, and the absorption of tranexamic acid from a larger segment of the gastrointestinal tract (i.e., both the stomach and the small intestine, rather than the stomach only or the lower portion of the small intestine if any modified release dosage form with a longer release time was used), preferably results in reduced levels of dissolved tranexamic acid in the region of the gastrointestinal tract proximal or distal to the dosage form. Reduced concentrations of tranexamic acid along the gastrointestinal tract preferably provide a reduction in adverse gastrointestinal effects associated with oral tranexamic acid therapy.

As used herein, alleviation of adverse effects using these formulations indicates any relief in one or more symptoms, such as decrease in incidence, severity, or duration of symptoms, and is not limited to absence of symptoms or elimination of symptoms. Thus, treatment includes any decrease in incidence, duration, intensity, frequency, etc. of adverse gastrointestinal symptoms including, but not limited to, headache, nausea, vomiting, diarrhea, constipation, cramping, bloating, and combinations thereof. The formulations may reduce symptoms at any time during tranexamic acid therapy, but minimized adverse effects are particularly noted immediately or shortly after dosing, that is, within the first few hours after dosing. As used herein, adverse gastrointestinal effects and side effects are used interchangeably to indicate nontherapeutic effects (i.e., not relating to any possible beneficial effects due to tranexamic acid), ranging from unpleasant but tolerable sensations to severe gastrointestinal symptoms. As used herein, the terms oral formulations, ingestable formulations, and orally administered formulations are used interchangeably and include any dosage forms which are ingested by mouth, including, but not limited to, tablets, pills, liquids, gelcaps, softgels, dragees, capsules, powders, granules, pellets, etc.

Modified release formulations of tranexamic acid include tablets, pellets, granules, capsules, or other oral dosage forms prepared in such a way to release tranexamic acid in a designed manner. In certain embodiments, the modified release material is a gel-forming polymer, a hydratable polymer, a water soluble polymer, a water swellable polymer, or mixtures thereof.

In certain embodiments, modified release tranexamic acid tablets are prepared by adding a modified release material comprising a gel-forming or hydratable polymer to a tranexamic tablet composition. Suitable gel-forming or hydratable polymers include, but are not limited to, hydroxyproplycellulose, hydroxypropylmethylcellulose or hypromellose, carboxymethylcellulose, polyvinyl alcohol, etc. This provides a compressed tablet that may or may not be film coated. The

tablet releases tranexamic acid by diffusion of tranexamic acid through the tablet matrix, or by erosion of the tablet matrix, or by a combination of diffusion from and erosion of the tablet matrix. Tablets formed with water swellable polymers release tranexamic acid by diffusion of tranexamic acid through the tablet matrix, or by erosion of the tablet matrix, or by a combination of diffusion from and erosion of the tablet matrix. One or more water-soluble hydrophilic polymer(s) may also be used. These include polyvinylpyrrolidine, hydroxypropyl cellulose, hydroxypropylmethylcellulose, now referred to as hypromellose (e.g., Methocel™, Dow Chemical Company), methyl cellulose, vinyl acetate/crotonic acid copolymers, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers, derivatives thereof and mixtures thereof. In various embodiments, the polymer is hydroxypropyl cellulose or hydroxypropylmethylcellulose. The polymer may be hydroxypropyl-methyl cellulose with a viscosity ranging from about 50 cps to about 200 cps. The polymer may be hydroxypropyl-methyl cellulose with a viscosity of 100 cps, commercially available as Methocel™ K 100 LV (Dow Chemical Company). The amount of polymer in the composition may be in the range of about 5% by weight to about 50% by weight of the composition. In various embodiments, the polymer is in the range of about 10% by weight to about 35% by weight of the composition, or about 10% by weight to about 30% by weight of the composition.

In certain embodiments the modified release material comprises a vinyl polymer, phthalic acid derivative of vinyl copolymer, hydroxyalkylcellulose, alkylcellulose (e.g., ethylcellulose), cellulose acetate, hydroxyalkylcellulose acetate, cellulose ether, alkylcellulose acetate and partial esters thereof, and polymers and copolymers of lower alkyl acrylic acids and lower alkyl acrylates and partial esters thereof, or combination thereof. In preferred embodiments the modified release material comprises hydroxypropylcellulose, hydroxpropylmethylcellulose, carboxymethylcellulose, polyvinyl alcohol, polyvinylpyrrolidone, methylcellulose, vinyl acetate/crotonic acid copolymers, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers, derivatives thereof, and mixtures thereof. In further preferred embodiments the modified release material comprises a polymer such as a methacrylic acid copolymer. These are copolymers of methacrylic acid with neutral acrylate or methacrylate esters such as ethyl acrylate or methyl methacrylate.

In certain embodiments the modified release material comprises a pH independent binder or film-forming agent such as hydroxypropyl methycellulose, hydroxypropyl cellulose, methylcellulose, polyvinylpyrrolidone, neutral poly(meth) acrylate esters (e.g., the methyl methacrylate/ethyl acrylate copolymers sold as Eudragit® (Rohm Pharma), starches, gelatin, sugars such as glucose, sucrose, and mannitol, silicic acid, carboxymethylcellulose, and the like, diluents such as lactose, mannitol, dry starch, microcrystalline cellulose and the like, surface active agents such as polyoxyethylene sorbitan esters, sorbitan ethers, and the like, coloring agents, flavoring agents, lubricants such as talc, calcium stearate, and magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and other tableting aids. Any combination of the aforementioned binders or film-forming agents may be included in the modified release material. The modified release material may be combined with tranexamic acid to form modified release dosage forms.

In certain embodiments, the formulation includes tranexamic acid in the range of about 50% by weight to about 95% or more by weight of the formulation. In other embodiments, tranexamic acid is in the range of about 60% by weight to about 90% by weight, or about 60% by weight to about 80% by weight of the formulation. The remaining weight may be made up of the modified release material and additional excipients.

To prepare modified release tablet formulations, the agent or modified release material to slow the release of tranexamic acid may be incorporated into the tablet matrix or coated onto the tablet surface or both. In certain embodiments, tablet formulations prepared are formulated by granulating a blend of powders of the modified release material. The powder blend is formed by combining portions of the powdered components that make up the tablet. These powders are intimately mixed by dry-blending. The dry blended mixture is granulated by wet mixing of a solution of a binding agent with the powder blend. The time for such wet mixing may be controlled to influence the dissolution rate of the formulation. For example, the total powder mix time, that is, the time during which the powder is granulated, may range from about 1 min to about 10 min, or from about 2 min to about 5 min. Following granulation, the particles are removed from the granulator and placed in a fluid bed dryer, a vacuum dryer, a microwave dryer, or a tray dryer for drying. Drying conditions are sufficient to remove unwanted granulating solvent, typically water, or to reduce the amount of granulating solvent to an acceptable level. Drying conditions in a fluid bed dryer or tray dryer are typically about 50 to 70° C. The granulate is dried, screened, mixed with additional excipients such as disintegrating agents, flow agents, or compression aids and lubricants such as talc, stearic acid, or magnesium stearate, and compressed into tablets.

In certain embodiments, the tablet that contains a modified release material within the tablet matrix may be coated with an optional film-forming agent. This applied film may aid in identification, mask an unpleasant taste, allow desired colors and surface appearance, provide enhanced elegance, aid in swallowing, aid in enteric coating, etc. The amount of film-forming agent may be in the range of about 2% tablet weight to about 4% tablet weight. Suitable film-forming agents are known to one skilled in the art and include hydroxypropyl cellulose, cellulose ester, cellulose ether, one or more acrylic polymer(s), hydroxypropyl methylcellulose, cationic methacrylate copolymers (diethylaminoethyl) methacrylate/methyl-butyl-methacrylate copolymers such as Eudragit E® (Rohm Pharma) and the like. The film-forming agents may optionally contain colorants, plasticizers, fillers, etc. including, but not limited to, propylene glycol, sorbitan monooleate, sorbic acid, titanium dioxide, and one or more pharmaceutically acceptable dye(s).

In certain embodiments, the tranexamic acid tablets of the invention are coated with a modified release material. In certain embodiments, tranexamic acid tablets are formulated by dry blending, rotary compacting, or wet granulating powders composed of tranexamic acid and tablet excipients. These powders are compressed into an immediate release tablet. Coating this immediate release tablet with a modified release material as described herein renders this tranexamic acid tablet as a modified release tablet.

In addition to the modified release material, the formulations of the invention may also contain suitable quantities of other materials, e.g. preservatives, diluents (e.g., microcrystalline cellulose), lubricants (e.g., stearic acid, magnesium stearate, and the like), binders (e.g., povidone, starch, and the like), disintegrants (e.g, croscarmellose sodium, corn starch, and the like), glidants (e.g., talc, colloidal silicon dioxide, and the like), granulating aids, colorants, and flavorants that are conventional in the pharmaceutical art. Specific examples of pharmaceutically acceptable excipients that may be used to formulate oral dosage forms are described in the Handbook of

Pharmaceutical Excipients, American Pharmaceutical Association (2003), incorporated by reference herein.

The release process may be adjusted by varying the type, amount, and the ratio of the ingredients to produce the desired dissolution profile, as known to one skilled in the art. A coating may be a partially neutralized pH-dependent binder that controls the rate of tranexamic acid dissolution in aqueous media across the range of pH in the stomach, which has a pH of about 2, and the intestine, which has a pH of about 5.5 in its upper region. In certain embodiments, one or more pH dependent binders may be used to modify the dissolution profile so that tranexamic acid is released slowly and continuously as the formulation passes through the stomach and/or intestines.

In one embodiment, compressed modified release tablets are formulated to comply with USP criteria and to be of such a size and shape to be easy to swallow. The size of the tablet will depend upon the dose of tranexamic acid that is needed to provide adequate therapy and the particular formulation and excipients that are selected to provide the physical properties necessary for tableting and for modified release. In various embodiments, a compressed modified release tablet contains from about 500 mg to about 1 gram of tranexamic acid, or from about 600 mg to about 750 mg of tranexamic acid. The daily dose of tranexamic acid may be achieved by taking one or two tablets at each dosing time.

In certain embodiments, the tranexamic acid included in the dosage form is from about 375 mg to about 1500 mg, preferably from about 375 mg to about 1000 mg. In one embodiment, the dose of tranexamic acid per tablet is in the range of about 500 mg to about 1000 mg for tablets and from about 500 mg to about 1500 mg for a sachet filled with granules. In another embodiment, the dose of tranexamic acid is in the range of about 3 grams/day to about 6 grams/day in three or four divided doses. As an example, a total daily dose of 3 grams tranexamic acid may be divided into three doses of one tablet each with each tablet containing 1 gram tranexamic acid, or may be divided into four doses of one tablet each with each tablet containing 0.75 gram tranexamic acid. As another example, a total daily dose of 4 gram tranexamic acid may be divided into three doses of two tablets at each dose with each tablet containing 0.666 gram tranexamic acid, or may be divided into four doses of one tablet each with each tablet containing 1 gram tranexamic acid. As another example, a total daily dose of 5 gram tranexamic acid may be divided into three doses of one tablet each with each tablet containing 1.66 gram tranexamic acid, or may be divided into four doses of two tablets each with each tablet containing 0.625 gram tranexamic acid. As another example, a total daily dose of 6 gram tranexamic acid may be divided into three doses of two tablets each with each tablet containing 1 gram tranexamic acid, or may be divided into four doses of two tablets each with each tablet containing 0.75 gram tranexamic acid. For ease of swallowing, the dose of tranexamic acid taken at each dosing time may be delivered by taking multiple tablets. For example, the 4 gram daily dose may be delivered by taking two 666.67 mg tablets three times a day or two 500 mg tablets four times a day. Similarly, the 3 gram daily dose may be achieved by taking two 550 mg tablets three times a day or two 375 mg tablets four times a day. Alternatively, for ease of reference, a dose of 600 mg, 650 mg, or 700 mg of tranexamic acid per tablet may be used. In a preferred embodiment, a total daily dose of 3900 mg/day is administered in three divided doses of 1300 mg of two tablets at each dose with each tablet containing 650 mg of tranexamic acid. Alternatively, each dose may be delivered by taking granules containing the prescribed amount of tranexamic acid presented in a convenient unit dose package. Such examples are not limiting and other doses within these ranges will be appreciated by those skilled in the art.

Since tranexamic acid is primarily eliminated via the kidneys by glomerular filtration with more than 95% excreted unchanged drug in the urine, dosage adjustment may be recommended. The table below lists some recommended dosage adjustments for renal impairment:

Serum Creatinine (mg/dl)	Estimated GFR* (ml/min)	Adjusted dose	Total daily dose
1.4 to 2.8	30-60	1.3 g (two 650 mg tablets) BID	2.6 g
2.8 to 5.7	15-30	1.3 g (two 650 mg tablets) QD	1.3 g
>5.7	<15	1.3 g (two 650 mg tablets) every 48 hours or 650 mg (one tablet) every 24 hours	0.65 g

Alternatively, modified release tranexamic acid formulations may be administered by pellets or granules in e.g., a sachet or capsule. Modified release tranexamic acid pellets or granules may be prepared by using materials to modify the release of tranexamic acid from the granule or pellet matrix. Modified release preparations may also be formulated using coatings to modify the release of tranexamic acid from the granule or pellet. U.S. Pat. Nos. 5,650,174; and 5,229,135 each of which is expressly incorporated by reference herein in its entirety, disclose variations on fabricating a pellet or nonpareil dosage form. Spheres are filled into packets, termed sachets, or capsules which are filled by weight to contain the prescribed dose of drug. Multiparticulates may be coated with an modified release coating, as disclosed in U.S. Pat. No. 6,066,339, which is expressly incorporated by reference herein its entirety. Coated multiparticulates may be packaged in capsules or sachets. The formulation of granules or pellets for modified release is described in Multiparticulate Oral Drug Delivery, Ghebre-Sellassie, Ed. in Drugs and the Pharmaceutical Sciences, Vol. 65 Marcel Dekker Inc. NY, 1994 and in the relevant parts of the references for modified release formulations previously cited and the relevant portions incorporated herein by reference.

Additional tranexamic acid formulations are disclosed in U.S. patent application Ser. Nos. 12/220,241, filed Jul. 23, 2008; and 11/346,710, filed Feb. 3, 2006, the disclosures of which are hereby incorporated by reference in their entirety.

In certain embodiments, the inventive tranexamic acid formulations may be used for additional indications other than menorrhagia, such as conization of the cervix, epistaxis, hyphema, hereditary angioneurotic edema, a patient with a blood coagulation disorder undergoing dental surgery, combinations thereof, and the like.

Menorrhagia Instrument

With regard to the treatment of menorrhagia (Heavy Menstrual Bleeding) studies of the safety and efficacy of the antifibrinolytic tranexamic acid were conducted. As part of these studies a diagnosis and treatment instrument (Menorrhagia Instrument; MI) was designed. The instrument reliably identifies and monitors heavy menstrual bleeding patients and can be used in conjunction with an antifibrinolytic agent to diagnose and monitor the treatment of heavy menstrual bleeding.

A Menorrhagia Instrument (MI) of the invention reliably captures the diagnosis and treatment of the disease by measuring the impact of treatment on the symptoms associated with heavy menstrual bleeding. The information obtained

from individual patient responses to the measures described in the methods of the present invention correlates to blood loss as measured by the alkaline hematin test. For example, data from the measures of social, leisure and/or physical activity symptoms, correlate with the volume of blood loss, and the change in the intensity of these symptoms correlates with the change in volume of blood lost, thus providing a measurement for the successful diagnosis and evaluation of treatment of bleeding disorders.

The instrument of the present invention measures specific aspects of the patient's monthly menstrual period. The measures correlate with the diagnosis of heavy menstrual bleeding and with the course of antifibrinolytic treatment. Further each of the measures individually correlate with quantity of blood loss as measured by the alkaline Hematin test. The symptomatic measures include: 1) a functional assessment measure; and ii) a pharmacology (or therapy assessment) measure.

The functional assessment measure of symptoms is further factored into segments which include 1) a measure of functional impairment generally; 2) impairment of necessary activities; and 3) impairment of discretionary activities.

The pharmacology domain provides an assessment of the severity of the menstrual period.

Specific symptomatic measures may be directed to an initial patient assessment and to the treatment period (pharmacology measure). Examples of specific measures would include examples of initial patient assessment measures (measures 1-4 listed in the Menorrhagia Instrument of FIG. 7); and therapy assessment measures (measures 1-4 together with measures 6, 6a, 6b and 6c contained in the Menorrhagia Instrument of FIG. 7).

In certain embodiments, the present invention is directed to a method of diagnosing and treating heavy menstrual bleeding, wherein the initial diagnoses of heavy menstrual bleeding is accomplished by evaluation of the most recent menstrual period on the basis of one, some or all of the prescribed symptomatic measures of FIG. 7. Measures which may be used as part of the initial patient assessment include, for example: a) determining a patient's perceived blood loss during their most recent menstrual period; b) determining how much the patient's blood loss limited their work outside and inside the home; c) determining how much the patient's blood loss limited their physical activities; d) determining how much the patient's blood loss limited their social and leisure activities; and e) determining the specific activities that were limited by the patient's blood loss.

The assessment of the patient's perceived blood loss during their most recent menstrual period may include an inquiry such as "during your most recent menstrual period, your blood loss was". The assessment may then quantify the patient response as a blood loss that was: i) light, ii) moderate, iii) heavy, or iv) very heavy. Alternatively, the measure may be quantified in terms of a scale of from one to four where one represents light, two represents moderate, three represents heavy and four represents very heavy.

The assessment of a patient's limitation due to the blood loss may include and evaluation of the patient's blood loss limitation on physical activities and/or how much the patient's blood loss limited their social and leisure activities. Assessment of the limitations on work, physical, social and leisure activities may be quantitated as: i) not at all, ii) slightly, iii) moderately, iv) quite a bit, or v) extremely. Alternatively the measure may be quantified in terms of a scale of from one to five where one represents not at all, two represents slightly, three represents moderately, four represents quite a bit, and five represents extremely.

Activities limited may include, but are not limited to, walking, standing, climbing stairs, squatting or bending down, playing with children and attending school activities. Home management activities include, but are not limited to, cooking, cleaning, yard work, and laundry. Leisure activities may include, but are not limited to, dancing, dinner, and movies. Sports activities may include, but are not limited to, tennis, golf, running, swimming, hiking, biking, boating, baseball, softball, basketball, soccer, fencing, volleyball, and other sports related activities.

Once the initial patient assessment measures have been completed and the patient has been identified as in need of treatment, the patient is administered a therapeutically effective treatment regimen of an antifibrinolytic agent. Suitable antifibrinolytic agents contemplated for use in the present invention include, but are not limited to tranexamic acid, aminocaproic acid, pharmaceutically acceptable salts, esters, derivatives, pro-drugs, metabolites, and analogues of any of the foregoing antifibrinolytic agents.

In certain embodiments the preferred antifibrinolytic agent is tranexamic acid. The tranexamic acid utilized in the present invention can be formulated into any suitable dosage form. Preferably, the tranexamic acid is in the form of a release modified tranexainic acid formulation.

When the preferred antifibrinolytic is tranexamic acid, the therapeutically effective treatment regimen contemplated by the present invention includes administration of a single dose of a tranexamic acid ranging from about 650 mg to about 1300 mg three (3) times a day for at least one day of menstruation, but not more than five days (or 15 single doses). The treatment regimen may be administered for at least one day; for at least the first two days, for at least the first three days, for days two through three, for days two to three, for the duration of menstruation.

In certain embodiments the tranexamic acid treatment regimen for treating the heavy menstrual bleeding includes administration of a single dose of about 650 mg to about 1.3 gm of a modified release formulation three (3) times a day, wherein the modified release formulation contains the tranexamic acid in combination with a modified release material

In certain other embodiments, the present invention is directed to a method of evaluating the effectiveness of a treatment regimen administered for heavy menstrual bleeding.

Evaluation of the effectiveness of the treatment regimen can be initiated at the end of the patient's menstrual period, but prior to completion of the menstrual cycle. The post-menstruation measures provide in part the pharmacology (or therapy assessment) measure described above.

The pharmacology assessment may begin with one or more of the same series of measures utilized during the initial patient assessment, which include: a) determining a patient's perceived blood loss volume during their most recent menstrual period; b) determining how much the patient's blood loss limited their work outside and inside the home; c) determining how much the patient's blood loss limited their physical activities; d) determining how much the patient's blood loss limited their social and leisure activities; e) determining the specific activities that were limited by the patient's blood loss.

Alternatively, an evaluation of the effectiveness of the treatment regimen may require determining the change in the patient's perceived blood loss during the most recent menstrual period in comparison to the blood loss during the patient's previous menstrual period, measure 1 of FIG. 7 and/or an assessment of the improvement achieved, measure 6 of FIG. 7.

For example, a change in the patients perceived blood loss of about one unit for example from "heavy" to "moderate" or from a score of 3 ("heavy") to a score of 2 ("moderate") would provide the basis for continued treatment. While a perceived loss of less than one unit would suggest either a discontinuation of treatment or a second course after which the evaluation would be reconsidered. Alternatively, or in addition to the blood loss assessment, the practitioner may rely on the assessment in which the comparison of perceived loss is assessed as: i) "about the same", ii) "better", and iii) "worse", as prescribed in measure 6 in FIG. 1. When a patient's response is "about the same", an alternative treatment regimen may be considered for the next menstrual period. The practitioner may also reconsider re-administering the same treatment regimen for an additional menstrual period and later re-evaluate. When a patient's response is "better", the assessment may continue by requiring the patient to provide further information about the improvement in menstrual bleeding. For example, the assessment may include "if your menstrual bleeding improved since your last period, please indicate how much" (measure 6b of the MI of FIG. 7). Answers to this inquiry about an improvement in menstrual bleeding may require the patient to provide an answer such as: i) a very great deal better; ii) a great deal better; iii) a good deal better; iv) an average amount better; v) somewhat better; vi) a little better; or vii) almost the same, hardly better at all. Alternatively the answers can be scaled on a seven unit scale where "a very great deal better" is assigned a value of 7 and "almost the same" is valued as 7.

When a patient's response to measure 6 is "worse", the inquiry continues by requiring the patient to provide further data characterizing the change in menstrual bleeding. For example, the inquiry may determine "if your menstrual period worsened since your last period, please indicate how much" (measure 6c of MI of FIG. 7). Data for this measure to a worsening in menstrual bleeding may require the patient to provide a ranking such as: i) "a very great deal worse"; ii) "a great deal worse"; iii) "a good deal worse"; iv) "an average amount worse"; v) "somewhat worse"; vi) "a little worse"; or vii) "almost the same, hardly worse at all". As before the answers may be scaled on a seven unit scale where −1 is "almost the same" and −7 is "a very great deal worse".

The comparison of perceived blood loss which results in an improvement of at least one unit as measured by measure 1 of FIG. 7 and/or an assessment of a perceived blood loss which is "better" as provided in measure six of FIG. 1 may proceed by assesing whether the improvement "was a meaningful or an important change" to the patient (measure 6c of MI of FIG. 7).

The information obtained about the "improvement" or "worsening" in menstrual bleeding allows the practitioner to make an evaluation of the effectiveness of the treatment regimen which correlates with the change in blood loss as measured by the alkaline hematin test and demonstrated with clinical trial data.

The method for evaluating the effectiveness of a treatment regimen of the present invention may be repeated after each menstrual period. The data obtained from the initial patient assessment and the subsequent pharmacology (therapy assessment) can be stored into a computer database and utilized for future diagnostic and/or evaluation purposes.

In certain other embodiments, the present invention is directed to a method of treating heavy menstrual bleeding. The method involving, evaluating symtomatic data gathered from the measures individually or collectively as described in FIG. 1. (items one through four and six as discussed above) to determine the need for therapy and then administering, to a patient in need, a therapeutically effective treatment regimen of an antifibrinolytic agent, e.g., a release modified tranexamic acid formulation, wherein the treatment regimen is to be administered for part or for the duration of menstruation, but no longer than 5 days during the patient's menstrual cycle.

The present invention is further described with regard to the following examples.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention will be further appreciated with respect to the following non-limiting examples. Other variations or embodiments of the invention will also be apparent to one of ordinary skill in the art from the above descriptions and examples. Thus, the forgoing embodiments are not to be construed as limiting the scope of this invention.

Example 1

Modified release 650 mg tranexamic acid tablets were prepared having the ingredients listed in the Table 1 below:

TABLE 1

Ingredient	Quantity per batch (kg)	Quantity per tablet (mg)
Active Ingredient		
Tranexamic Acid, EP	84.50	650.0
Inactive Ingredients		
Microcrystalline Cellulose NF (Avicel PH 101)	5.753	44.25
Colloidal Silicon Dioxide NF	0.0975	0.75
Pregelatinized Corn Starch, NF	6.435	49.50
Hypromellose, USP (Methocel K3 Premium LV)	19.110	147.00
Povidone, USP (K value range 29-32)	4.680	36.00
Stearic Acid, NF (powder)	2.340	18.00
Magnesium Stearate, NF (powder)	0.585	4.50
Purified Water USP*	17.550	135.00

*Purified water is removed during processing

The formulation of Example 1 was prepared as follows:

1. Weigh all ingredients and keep in moisture resistant containers until ready for use.
2. Measure water into a container. Mix povidone at medium speed until completely dissolved.
3. Add tranexamic acid, microcrystalline cellulose (MCC), pregelatinized corn starch, and colloidal silicon dioxide to the high shear mixer.
4. Mix using impeller only.
5. Mix for an additional time (impeller only). Add all of the povidone solution during this mixing step.
6. Mix until adequately granulated (impeller and chopper). Proceed only when desired granulation has been achieved. Add additional water if necessary.
7. Dry the granulation to moisture content of NMT 1.2%.
8. Pass the granulation through the oscillating granulator equipped with a #30 mesh screen. Weigh the granulation. Add granulation to the V-Blender.
9. Add the hypromellose USP Methocel K3 Premium to the V-blender. Blend.
10. Pass magnesium stearate and stearic acid through oscillating granulator equipped with a #40 mesh screen. Add magnesium stearate and stearic acid to the V-blender and blend.
11. Perform specified physical property testing. Proceed to compression.
12. Compress tablets to desired weight.

Example 2

In Example 2, immediate release 650 mg tranexamic acid tablets were prepared having the ingredients listed in Table 2 below:

TABLE 2

Ingredient	Quantity per batch (kg)	Quantity per tablet (mg)
Active Ingredient		
Tranexamic Acid, EP (650 mg/tab)	84.50	650.0
Inactive Ingredients		
Microcrystalline Cellulose, NF (Avicel PH 101)	5.753	44.25
Microcrystalline Cellulose, NF (Avicel PH 102)	10.660	82.00
Colloidal Silicon Dioxide, NF	0.0975	0.75
Pregelatinized Corn Starch, NF	6.435	49.50
Croscarmellose Sodium, NF	19.50	15.00
Povidone, USP (K value range 29-32)	4.680	36.00
Stearic Acid, NF (powder)	2.340	18.00
Magnesium Stearate, NF (powder)	0.585	4.50
Purified Water, USP*	17.550	135.00
Film Coating (Inactive Ingredients)**		
Opadry White YS-1-7003	4.110	—
Purified Water, USP	36.990	—

*Purified water is removed during processing
**6 kg excess prepared to account for losses during transfer

The formulation of Example 2 was prepared as follows:

1. Weigh all ingredients and keep in moisture resistant containers until ready for use.
2. Measure water into a container. Mix povidone at medium speed until completely dissolved.
3. Add tranexamic acid, microcrystalline cellulose (MCC), pregelatinized corn starch, and colloidal silicon dioxide to the high shear mixer.
4. Mix using impeller only.
5. Mix for an additional time (impeller only). Add all of the povidone solution during this mixing step.
6. Mix until adequately granulated (impeller and chopper). Proceed only when desired granulation has been achieved. Add additional water if necessary.
7. Dry the granulation to moisture content of NMT 1.2%.
8. Pass the granulation through the oscillating granulator equipped with a #30 mesh screen. Weigh the granulation. Add granulation to the V-Blender.
9. Add the croscarmellose sodium and MCC to the V-Blender and blend.
10. Pass magnesium stearate and stearic acid through oscillating granulator equipped with a #40 mesh screen. Add magnesium stearate and stearic acid to the V-blender and blend.
11. Perform specified physical property testing. Proceed to compression.
12. Compress tablets.
12. After compression, spray coat the compressed dosage forms with the Opadry White in water.

Example 3

In Example 3, modified release 650 mg tranexamic acid tablets were prepared as in Example 1 and coated with a film coating similar to the immediate release tablets of Example 2. The ingredients are listed in Table 3 below:

TABLE 3

Ingredient	Quantity per batch (kg)	Quantity per tablet (mg)
Active Ingredient		
Tranexamic Acid, EP	84.50	650.0
Inactive Ingredients		
Microcrystalline Cellulose NF (Avicel PH 101)	5.753	44.25
Colloidal Silicon Dioxide NF	0.0975	0.75
Pregelatinized Corn Starch, NF	6.435	49.50
Hypromellose, USP (Methocel K3 Premium LV)	19.110	147.00
Povidone, USP (K value range 29-32)	4.680	36.00
Stearic Acid, NF (powder)	2.340	18.00
Magnesium Stearate, NF (powder)	0.585	4.50
Purified Water USP*	17.550	135.00
Film Coating (Inactive Ingredients)**		
Opadry White YS-1-7003	4.305	—
Purified Water, USP	38.750	—

*Purified water is removed during processing
**6 kg excess prepared to account for losses during transfer

Example 3A

Example 3A, delayed release 650 mg tranexamic acid tablets were prepared having the ingredients listed in Table 3A below:

TABLE 3A

Ingredient	Quantity per batch (kg)	Quantity per tablet (mg)
Active Ingredient		
Tranexamic Acid, EP	84.50	650.0
Inactive Ingredients		
Microcrystalline Cellulose NF (Avicel PH 101)	5.753	44.25
Microcrystalline Cellulose NF (Avivel PH 102)	10.660	82.00
Colloidal Silicon Dioxide NF	0.0975	0.75
Pregelatinized Corn Starch, NF	6.435	49.50
Croscarmellose Sodium NF	19.50	15.00
Povidone, USP (K value range 29-32)	4.680	36.00
Stearic Acid, NF (powder)	2.340	18.00
Magnesium Stearate, NF (powder)	0.585	4.50
Purified Water USP*	17.550	135.00
Film Coating (Inactive Ingredients)**		
Acryl-Eze (930185359)	12.90	—
Silicone Emulsion, 30%	0.323	—
Purified Water, USP	51.271	—

*Purified water is removed during processing; mg per tablet is based on theoretical specific gravity of 1.0 g/ml
**6 kg excess prepared to account for losses during transfer

The formulation of Example 3A was prepared as follows:

1. Weigh all ingredients and keep in moisture resistant containers until ready for use.
2. Measure water into a container. Mix povidone at medium speed until completely dissolved.
3. Add tranexamic acid, microcrystalline cellulose (MCC), pregelatinized corn starch, and colloidal silicon dioxide to the high shear mixer.
4. Mix using impeller only.
5. Mix for an additional time (impeller only). Add all of the povidone solution during this mixing step.
6. Mix until adequately granulated (impeller and chopper). Proceed only when desired granulation has been achieved. Add additional water if necessary.

7. Dry the granulation to moisture content of NMT. 1.2%.
8. Pass the granulation through the oscillating granulator equipped with a #30 mesh screen. Weigh the granulation. Add granulation to the V-Blender.
9. Add the croscarmellose sodium and MCC to the V-Blender and blend.
10. Pass magnesium stearate and stearic acid through oscillating granulator equipped with a #40 mesh screen. Add magnesium stearate and stearic acid to the V-blender and blend.
11. Perform specified physical property testing. Proceed to compression.
12. Compress tablets.
13. After compression, spray coat the compressed dosage forms with the film coating.

Dissolution results for the delayed release formulation of Example 3A (in base stage) are listed below in Table 3B.

Dissolution Results for the Delayed Release Formulation (in Base Stage)

TABLE 3B

Time (min.)	Dissolution (%)	Standard Deviation
15	16%	±6.013873
30	89%	±14.06769
45	95%	±2.810694
60	97%	±2.345208

Example 4

Bioavailability and Bioequivalence Evaluation

In Example 4, a comparative, randomized, single dose, 4-way Crossover Absolute Bioavailability (BA) and Bioequivalence (BE) study of Tranexamic Acid Tablet Formulations prepared in accordance with Examples 1 and 2 in Healthy Adult Women Volunteers under Fasting Conditions was performed. The objective was to assess the bioequivalence of a 650 mg modified release tablet formulation prepared in accordance with Example 1 compared to the immediate release reference tablet formulation of tranexamic acid prepared in accordance with Example 2, and to determine the bioavailability of the modified tablet formulation to the approved IV (1 g) formulation Cyklokapron® by Pharmacia & Upjohn. The design was a randomized, 4-way crossover, comparative BE and BA determination. All oral doses administered were 1.3 g. Twenty-eight (28) healthy non-smoking adult female volunteer subjects were enrolled in the study. A total of 26 subjects completed the study. Sample size was calculated assuming a 25% CV in AUC_{inf}. The study endpoints were the 90% confidence intervals of the ratio of least-squares means of the pharmacokinetic parameters AUC_{0-t}, AUC_{inf} and C_{max} of the modified release formulation to the immediate-release formulation from serum concentration-time data drawn up to 36 hours after a single dose of drug. In addition, the bioavailability of the tablet formulations were calculated. Smokers, oral contraceptive users, those with a previous history of thromboembolic events and altered vision were excluded from the study. ECG monitoring was performed before, during and after the estimated times of peak serum tranexamic acid concentrations exposure. Adverse events were captured and recorded throughout the trial period.

In the study, subjects were randomized to receive single oral 1.3 g (2×650 mg tablets) dose of tranexamic acid in tablet forms which included a modified release dosage form and an immediate release dosage form. Subjects were also administered a single 1 g (10 ml) IV solution of tranexamic acid (100 mg/ml concentration).

A summary of the pharmacokinetic results from the study of Example 4 are listed in the tables below.

TABLE 4

Summary of Results - Tranexamic Acid in Plasma
Pharmacokinetic Parameters (N = 26)

	ln AUC 0-t* (mcg · h/mL)	ln AUCinf* (mcg · h/mL)	ln Cmax* (mcg/mL)
Modified Release formulation			
Mean	66.703	69.642	11.251088
CV	26.8	27.2	29.1
N	26	24	26
Immediate Release formulation			
Mean	70.157	72.656	12.260414
CV	16.2	16.4	23.0
N	26	24	26
Least-Squares Mean:			
Modified Release	66.935	68.891	11.321919
Immediate Release	70.051	72.411	12.258222
Ratio of Least-Squares Mean (modified release/immediate release)%	95.6	95.1	92.4

*For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.

AUCinf, kel, half-life and F could not be estimated for some subjects.

AUC 0-t is the area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.

TABLE 5

Summary of Results - Tranexamic Acid in Plasma
Pharmacokinetic Parameters
(N = 26)

	Tmax (h)	Half-life (h)	kel (1/h)	F (%)
Modified Release formulation				
Mean	2.942	11.370	0.06300	44.93
CV	22.7	17.6	19.4	25.3
n	26	26	26	24
Immediate Release formulation				
Mean	2.808	11.013	0.06438	46.04
CV	20.8	15.5	15.3	16.1
n	26	24	24	24

TABLE 6

Summary of Results - Tranexamic Acid in Plasma Pharmacokinetic Parameters (N = 26)

	Ln AUC 0-t* (mcg · h/mL)	ln AUCinf* (mcg · h/mL)	ln Cmax* (mcg/mL)
90% Confidence Intervals (Modified release/Immediate release)%			
lower limit:	87.8%	87.4%	84.0%
upper limit:	104.0%	103.5%	101.6%
p-Value (ANOVA)			
Modified vs Immediate	0.3721	0.3259	0.1676
Period	0.0704	0.0499	0.0356
Sequence	0.7734	0.7978	0.8207
Intrasubject CV %	18.3	17.4	20.6

*For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
AUCinf, kel, half-life and F could not be estimated for some subjects.

Concentration-time profiles for the study of Example 4 are presented on semi-log and linear scale over 36 hours and are depicted in FIGS. 3 and 4.

The following pharmacokinetic parameters in the table below were calculated for tranexamic acid in plasma for the study of Example 4.

MRT: The mean residence time (MRT) after intravenous administration of tranexamic acid was determined using the equation,

AUMC/AUC+infusion time/2,

where the AUMC is the area under the moment-time curve.

MTT: Following oral administration of the Modified Release and Immediate Release formulations, the mean transit time (MTT) of tranexamic acid was calculated by dividing the AUMC by the AUC.

MAT: The mean absorption time (MAT) for the two formulations was derived by subtracting the MRT from the MTT.

Mean (±SD) results are presented in the table below:

TABLE 7

	IV	Modified Release	Immediate Release
MRT (hours)	3.51 ± 0.38	N/A	N/A
MTT (hours)	N/A	7.70 ± 0.72	7.21 ± 1.01
MAT (hours)	N/A	4.18 ± 0.70	3.70 ± 0.94

The mean transit time (MTT) and mean absorption time (MAT) of the Modified Release formulation of tranexamic acid was approximately 30 minutes longer than that observed for the Immediate Release formulation.

The most frequently reported adverse events from the study of Example 4 are listed in the table below. The table lists the number of subjects reporting adverse events, and the percentage of subjects is in parentheses.

TABLE 8

	Treatment		
Adverse Events	Modified Release (2 × 650 mg) (n = 27)	Immediate Release (2 × 650 mg) (n = 27)	IV solution (10 × 100 mg/ml) (n = 27)
Headache	4 (15%)	7 (26%)	7 (26%)
Nausea	0 (0%)	2 (7%)	10 (37%)
Dizziness	0 (0%)	0 (0%)	11 (41%)
Feeling Hot	0 (0%)	0 (0%)	6 (22%)
Nasal Congestion	2 (7%)	1 (4%)	1 (4%)
Cough	0 (0%)	0 (0%)	2 (7%)
Urine odor abnormal	2 (7%)	0 (0%)	1 (4%)

Dissolution Results for Immediate Release and Modified Release Formulations prepared in accordance with Examples 2 and 1 respectively used in the study of Example 4 tested under USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. are listed in the tables below.

TABLE 9

Dissolution Results for the Immediate Release Formulation in Table 2.

Time (min.)	Dissolution (%)	Standard Deviation
15	58.0%	±9.521905
30	96.0%	±10.2697
45	102.0%	±0.408248
60	104.0%	±1.032796

TABLE 10

Dissolution Results for the Modified Release Formulation in Table 1

Time (min.)	Dissolution (%)	Standard Deviation
15	21.0%	±1.414214
30	40.0%	±2.810694
45	58.0%	±3.600926
60	73.0%	±3.81663
90	98.0%	±2.097618

TABLE 10A

Dissolution Results for the Various Batches of the Modified Release Formulation Table 1

Batch #	0 min	15 min	45 min	90 min		Standard Deviation		
Batch 1	0	21	58	98	0	±1.386	±3.48	±2.254
Batch 2	0	21	58	95	0	±1.134	±3.074	±2.47
Batch 3	0	23	59	93	0	±2.323	±4.366	±3.627
Batch 4	0	21	56	89	0	±1.575	±3.808	±2.492
Batch 5	0	24	59	93	0	±2.016	±3.422	±2.139
Batch 6	0	25	67	100	0	±1.45	±3.149	±0.9
Batch 7	0	22	58	94	0	±0.968	±2.32	±2.068
Batch 8	0	29	69	98	0	±2.03	±3.726	±1.666
Batch 9	0	28	66	96	0	±2.268	±3.762	±2.688
Batch 10	0	15	65	93	0	±1.904	±2.47	±2.604
Batch 11	0	27	64	92	0	±1.836	±2.368	±2.024

Conclusions

The ratios of least-squares means and the 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC_{0-t}, AUC_{inf} and C_{max} for tranexamic acid in plasma were within the 80-125% Food and Drug Administration (FDA) acceptance range for the modified release formulation versus the immediate release formulation under fasting conditions.

The absolute bioavailability of the modified release and immediate release tablet formulations were 44.93% and 46.04% respectively.

Based on these results, the modified release tranexamic acid tablet formulation and the immediate release tranexamic acid formulation are bioequivalent under fasting conditions.

Example 4A

Comparative Example

In Comparative Example 4A, a 500 mg immediate release tranexamic acid tablet, approved and marketed in Canada under the name Cyklokapron was obtained and dissolution tested under USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. The dissolution results are listed in Table 10A below:

TABLE 10A

Sample #	% dissolved in 15 min.	% dissolved in 30 min.	% dissolve in 45 min.	% dissolved in 60 min.
1	102	104	105	106
2	102	104	105	106
3	101	102	102	105
4	99	101	102	103
5	100	102	103	104
6	99	101	102	104
Average	101	102	103	105
% RSD	1.4	1.3	1.4	1.1

Example 5

In Example 5, based on single dose pharmacokinetic parameters, pharmacokinetic simulations of serum concentrations were performed to compare dosing the modified release formulation of Example 4 at every 8 hours (Q8H: at 6:00 AM, 2:00 PM, 10:00 PM) and dosing three times a day, other than every 8 hours (TID: at 8:00 AM, 2:00 PM, and 10:00 PM). The results are provided in Tables 11-14 below.

TABLE 11

Tranexamic Acid - Modified Release Formulation
Dosage Regimen Simulation - ORAL
1.3 g q8 hr

Time (h)	Dose(mcg)	Conc.(mcg/mL)
0	1.30E+06	0
1	0	4.0594
2	0	10.0551
3	0	10.6433
4	0	9.20306
5	0	7.26932
6	0	5.4699
8	1.30E+06	2.89909
9	0	6.15391
10	0	11.5813
11	0	11.7752
12	0	10.0646
13	0	7.94622
14	0	6.02067
15	0	4.4712
16	1.30E+06	3.30248
17	0	6.51406
18	0	11.9097
19	0	12.0794
20	0	10.3495
21	0	8.21523
22	0	6.2761
23	0	4.71463

TABLE 11-continued

Tranexamic Acid - Modified Release Formulation
Dosage Regimen Simulation - ORAL
1.3 g q8 hr

Time (h)	Dose(mcg)	Conc.(mcg/mL)
24	1.30E+06	3.53505
25	0	6.73663
26	0	12.1229
27	0	12.2838
28	0	10.5455
29	0	8.40336
30	0	6.45664
31	0	4.88791
32	1.30E+06	3.70138
33	0	6.89628
34	0	12.2762
35	0	12.4309
36	0	10.6868
37	0	8.53894
38	0	6.5868
39	0	5.01286
40	1.30E+06	3.82133
41	0	7.01144
42	0	12.3867
43	0	12.537
44	0	10.7887
45	0	8.63675
46	0	6.68069
47	0	5.103
48	1.30E+06	3.90786
49	0	7.09451
50	0	12.4665
51	0	12.6136
52	0	10.8621
53	0	8.70731
54	0	6.74842
55	0	5.16802
56	1.30E+06	3.97028
57	0	7.15443
58	0	12.524
59	0	12.6688
60	0	10.9152
61	0	8.7582
62	0	6.79728
63	0	5.21493
64	1.30E+06	4.01531
65	0	7.19766
66	0	12.5655
67	0	12.7087
68	0	10.9534
69	0	8.79492
70	0	6.83253
71	0	5.24877
72	1.30E+06	4.0478
73	0	7.22885
74	0	12.5954
75	0	12.7374
76	0	10.981
77	0	8.82141
78	0	6.85796
79	0	5.27318
80	1.30E+06	4.07124
81	0	7.25135
82	0	12.617
83	0	12.7581
84	0	11.0009
85	0	8.84052
86	0	6.87631
87	0	5.29079
88	1.30E+06	4.08814
89	0	7.26758
90	0	12.6326
91	0	12.7731
92	0	11.0153
93	0	8.8543
94	0	6.88954
95	0	5.3035

TABLE 11-continued

Tranexamic Acid - Modified Release Formulation
Dosage Regimen Simulation - ORAL
1.3 g q8 hr

Time (h)	Dose(mcg)	Conc.(mcg/mL)
96	1.30E+06	4.10034
97	0	7.27929
98	0	12.6439
99	0	12.7839
100	0	11.0256
101	0	8.86425
102	0	6.89909
103	0	5.31266
104	1.30E+06	4.10913
105	0	7.28773
106	0	12.652
107	0	12.7917
108	0	11.0331
109	0	8.87142
110	0	6.90597
111	0	5.31927
112	1.30E+06	4.11548
113	0	7.29382
114	0	12.6578
115	0	12.7973
116	0	11.0385
117	0	8.8766
118	0	6.91094
119	0	5.32404
120	0	4.12006

Concentration-time profiles are presented over 120 hours for the modified release formulation in Table 12 and are depicted in FIG. **1**. A 1 g formulation administered q8h is also depicted for comparison purposes.

TABLE 12

Cmax, Cmin and Cavg for 1.3 g q8 hr simulation
Simulation at 120 hours

Pharmacokinetic Parameter	Concentration
Cmax	12.8 mcg/mL
Cmin	4.1 mcg/mL
Cavg	8.4 mcg/ml

TABLE 13

Tranexamic Acid - Modified Release Formulation
Dosage Regimen Simulation - ORAL
1.3 g TID (8:00 AM, 2:00 PM, and 10:00 PM)

Time (h)	Dose (mcg)	Conc. (mcg/mL)
0	1.30E+06	0
1	0	4.0594
2	0	10.0551
3	0	10.6433
4	0	9.20306
5	0	7.26932
6	1.30E+06	5.4699
8	0	12.9542
9	0	12.7378
10	0	10.7293
11	0	8.40129
12	1.30E+06	6.33141
13	0	8.74352
14	0	13.505
15	0	13.2018
16	0	11.1327
17	0	8.76144
18	0	6.65976
19	0	4.98823

TABLE 13-continued

Tranexamic Acid - Modified Release Formulation
Dosage Regimen Simulation - ORAL
1.3 g TID (8:00 AM, 2:00 PM, and 10:00 PM)

Time (h)	Dose (mcg)	Conc. (mcg/mL)
20	0	3.73474
21	0	2.8275
22	0	2.18502
23	0	1.73555
24	1.30E+06	1.42243
25	0	5.26298
26	0	11.104
27	0	11.5807
28	0	10.058
29	0	8.06103
30	1.30E+06	6.21137
31	0	8.76659
32	0	13.6187
33	0	13.3709
34	0	11.334
35	0	8.97998
36	1.30E+06	6.88576
37	0	9.27495
38	0	14.0147
39	0	13.6908
40	0	11.6019
41	0	9.21185
42	0	7.09208
43	0	5.40321
44	0	4.1331
45	0	3.20991
46	0	2.55212
47	0	2.08796
48	1.30E+06	1.76074
49	0	5.58776
50	0	11.4158
51	0	11.88
52	0	10.3453
53	0	8.33688
54	1.30E+06	6.47618
55	0	9.02081
56	0	13.8627
57	0	13.6052
58	0	11.5589
59	0	9.1959
60	1.30E+06	7.09304
61	0	9.47395
62	0	14.2057
63	0	13.8742
64	0	11.778
65	0	9.38036
66	0	7.25433
67	0	5.55898
68	0	4.28264
69	0	3.35346
70	0	2.68993
71	0	2.22026
72	1.30E+06	1.88775
73	0	5.70968
74	0	11.5329
75	0	11.9924
76	0	10.4532
77	0	8.44044
78	1.30E+06	6.57559
79	0	9.11625
80	0	13.9543
81	0	13.6931
82	0	11.6434
83	0	9.27696
84	1.30E+06	7.17086
85	0	9.54865
86	0	14.2775
87	0	13.943
88	0	11.8441
89	0	9.44431
90	0	7.31525
91	0	5.61745
92	0	4.33877
93	0	3.40735

TABLE 13-continued

Tranexamic Acid - Modified Release Formulation Dosage Regimen Simulation - ORAL 1.3 g TID (8:00 AM, 2:00 PM, and 10:00 PM)		
Time (h)	Dose (mcg)	Conc. (mcg/mL)
94	0	2.74167
95	0	2.26992
96	1.30E+06	1.93543
97	0	5.75546
98	0	11.5768
99	0	12.0346
100	0	10.4937
101	0	8.47931
102	1.30E+06	6.61292
103	0	9.15208
104	0	13.9887
105	0	13.7261
106	0	11.6751
107	0	9.30739
108	1.30E+06	7.20008
109	0	9.5767
110	0	14.3044
111	0	13.9689
112	0	11.8689
113	0	9.46813
114	0	7.33811
115	0	5.63941
116	0	4.35985
117	0	3.42759
118	0	2.76109
119	0	2.28857
120	0	1.95333

Concentration-time profiles are presented over 120 hours for the modified release formulation in Table 14 and are depicted in FIG. **2**. A 1 g formulation administered TID is also depicted for comparison purposes.

TABLE 14

Cmax, Cmin and Cavg for 1.3 g TID (8:00 AM, 2:00 PM, and 10:00 PM) Simulation at 120 hours	
Pharmacokinetic Parameter	Conc.
Cmax	12.0, 14.0, 14.3 mcg/mL
Cmin	1.9, 6.6, 7.2 mcg/mL
Cavg	8.4 mcg/mL

Example 6

In Example 6, a study of a single dose followed by multiple doses, was performed on 20 healthy non-smoking adult female volunteers using a modified release formulation prepared in accordance with Example 1. After an overnight fast, subjects received a single oral dose of tranexamic acid (1.3 g) on Day 1. Blood samples were taken before dosing and up to 36 hours post-dose. Subjects received another single oral dose of tranexamic acid (1.3 g) on the evening of Day 2, and 3 times a day (every 8 hours) starting on the morning of Day 3 until the last dose on the morning of Day 7. Blood samples were taken before the 6th, 9th, 12th and 15th dose (the last dose) for the determination of C_{min}, and up to 8 hours after the last dose, for the determination of drug concentration at steady-state. Subjects were housed from at least 10 hours before the 1st dose on Day 1 until after the 8-hour blood draw following the 15th dose (on Day 7).

Tranexamic acid is minimally bound (approximately 3%) to plasma proteins (mainly plasminogen) at "typical" therapeutic plasma concentrations of approximately 5-15 mg/L. The main route of elimination of tranexamic acid is renal glomertular filtration. After oral administration of tranexamic acid (250 or 500 mg) to healthy adults, between 40-70% of the administered dose is excreted unchanged in the urine within 24 hours. After IV administration (1 g) 30% of the dose is excreted unchanged in the urine within one hour, 45-55% within 2-3 hours and 90% within 24 hours.

The beta elimination half-life of tranexamic acid is 2 hours. Based on published data, the mean C_{max} and AUC_{0-6} pharmacokinetic parameters after a single 1.3 g oral dose of tranexamic acid are expected to be approximately 65% of those achieved with a 2 g dose (i.e. ~10 mg/L and ~40 mg-h/L, C_{max} and AUC_{0-6} under fasting conditions, respectively).

However, the pharmacokinetics of tranexamic acid were not adequately characterized in Pilbrant, et al., *Eur. J. Clin. Pharmacol*, (1981)-20:65-72, since blood samples were collected for up to only 6 hours post-dose. In addition, the plasma concentration-time curves after IV administration showed three exponential phases, with a gamma elimination half-life of approximately 7 hours. For this reason, the concentration-time profile of tranexamic acid was estimated by simulating the data over 36 hours, after oral administration of a 1.3 g dose under fasting conditions, using NONMEM. Based on the simulation results, it would be appropriate to collect blood samples until 36 hours in order to characterize the AUC, Cmax, tmax, t½ and F.

The objective of this study of Example 6 was to assess the pharmacokinetic linearity of the test tablet formulation of tranexamic acid (modified release), after a single oral dose (Day 1) compared to a daily (1.3 g every 8 hours) dosage regimen (Days 2 to 7), under fasting conditions.

In the study of Example 6, blood samples (1×5 mL) were collected in blood collection tubes containing lithium heparin at Hour 0 (pre-dose) on Day 1, and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 14, 24, 28, 32, and 36 hours post-dose. Blood samples for Cmin determinations were also collected immediately before the 6th, 9th, 12th, and 15th doses on Days 4, 5, 6, and 7, respectively, and at the following times after the 15th dose: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, and 8 hours. Plasma samples were separated by centrifugation, then frozen at −20° C.±10° C. and kept frozen until assayed at AAI Development Services in New-Ulm, Germany.

Noncompartmental Pharmacokinetic Parameters

Calculations for plasma tranexamic acid were calculated by noncompartmental methods using the following pharmacokinetic parameters in Tables 15 and 16:

Day 1:

TABLE 15

AUC 0-t:	The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.
AUCinf:	The area under the plasma concentration versus time curve from time 0 to infinity. AUCinf was calculated as the sum of AUC 0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.
AUC/AUCinf:	The ratio of AUC 0-t to AUCinf.
Cmax:	Maximum measured plasma concentration over the time span specified.
tmax:	Time of the maximum measured plasma concentration. If the maximum value occured at more than one time point, tmax was defined as the first time point with this value.
kel:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. This parameter was calculated by linear least squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g. three or more non-zero plasma concentrations).
t½:	The apparent first-order terminal elimination half-life was calculated as 0.693/kel.

No value for kel, AUCinf or t½ were reported for cases that did not exhibit a terminal log-linear phase in the concentration versus time profile.

Day 7:

TABLE 16

AUCτ:	The area under the plasma concentration versus time curve over the final dosing interval, as calculated by the linear trapezoidal method.
Cmax:	Maximum measured plasma concentration over the final dosing interval.
Cmin:	Measured plasma concentration prior to the morning dose.
tmax:	Time of the maximum measured plasma concentration over the final dosing interval. If the maximum value occured at more than one time point, tmax was defined as the first time point with this value.
Flux:	Percent fluctuation was calculated as follows: Flux 1: $\frac{Cmax-Cmin}{Cssav}\times 100$ where Cssav was calculated as the ratio of AUC 0-τ to the dosing interval, τ. Flux 2: $\frac{Cmax-Cmin}{Cmin}\times 100$

Compartmental Pharmacokinetic Parameters

Compartmental analysis was performed on tranexamic acid data following single and multiple oral administrations of the modified release (MR) tablet formulation. Multiple compartmental models were constructed and their ability to fit plasma concentrations of tranexamic acid were evaluated using a standard two-stage (STS) approach with ADAPT-II (maximum likelihood analysis). The discrimination process was performed by computing the Akaike Information Criterion Test (AIC), the minimum value of the objective function (OBJ) and by looking at pertinent graphical representations of goodness of fit (e.g. fitted and observed concentrations versus time).

The final analysis was performed using an iterative two-stage approach with the IT2S® software. This software uses a population methodology which allows one to provide robust PK parameter estimates on an individual subject and population basis. All relevant pharmacokinetic parameters were calculated and reported. Concentrations were modeled using a weighting procedure of $W_j=1/S_j^2$ where the variance σj^2 was calculated for each observation using the equation $\sigma j^2-(a+b*Y_j)^2$ where a and b are the intercept and slope of each variance model. The slope is the residual variability associated with each concentration (includes the intra-individual variability and the sum of all experimental errors), and the intercept is related to the limit of detection of the analytical assay. All PK parameter estimates were updated iteratively during the population PK analysis (VARUP, IT2S®) until stable values were found. The analysis included the quantitative estimation of population PK parameters and interindividual variability of tranexamic acid in plasma.

Individual profiles of observed vs fitted plasma concentrations of tranexamic acid were provided for the MR formulation.

Statistical Analyses

Descriptive Statistics

Descriptive statistics including arithmetic means, standard deviations and coefficients of variation were calculated on the individual concentration and pharmacokinetic data. Additionally, geometric means were calculated for the parameters AUC_{0-t}, AUC_{inf}, and C_{max} for Day 1 and AUCτ, C_{max} and C_{min} for Day 7.

Time Dependence Pharmacokinetic Linearity

The pharmacokinetic parameter AUCτ (Day 7) was compared against AUC_{inf} (Day 1) using an analysis of variance (ANOVA) on the ln-transformed values for tranexamic acid. The ANOVA model included Group, Day (1 (AUC_{inf}) and 7 (AUCτ)) and the interaction Day*Group as fixed effects. All the interaction terms were not statistically significant, at a level of 5%, and were dropped from the final model. The ANOVA included calculation of least-squares means (LSM), the difference between Day LSM and the standard error associated with this difference. The above statistical analysis was done using the SAS® GLM procedure.

The ratio of LSM was calculated using the exponentiation of the Day LSM from the analysis on the ln-transformed response. The ratio was expressed as a percentage relative to AUC_{inf} (Day 1).

A ninety percent confidence interval for the ratio was derived by exponentiation of the confidence interval obtained for the difference between, Day LSM resulting from the analysis on the ln-transformed response. The confidence interval was expressed as a percentage relative to AUC_{inf} (Day 1).

Steady-State Analysis

A steady-state analysis was performed, on the ln-transformed pre-dose C_{min} concentrations at −72, −48, −24 and 0-hour time points, using Helmert's contrasts. The ANOVA model included Group, Time and the interaction Time*Group as fixed effects. In order to model the correlations within every subject, an appropriate variance-covariance matrix was chosen among the following: unstructured (UN), compound symmetry (CS), compound symmetry heterogeneous (CSH), variance component (VC), autoregressive (AR(1)), autoregressive heterogeneous (ARH(1)) and autoregressive moving average (ARMA(1,1)), using the Akaike's Burnham and Anderson criterion (AICC). All the interaction terms were not statistically significant, at a level of 5%, and were dropped from the final model. The ANOVA included also calculation of least-squares means (LSM) for each pre-dose C_{min} concentrations. Helmert's contrasts were constricted such that each time point is compared to the mean of subsequent time points. There are 3 contrasts associated to the 4 pre-dose concentration timepoints. They are listed in Table 17 below:

TABLE 17

Contrast	Tests
Compar. 1	Predose Day 4 compared to (mean predose of Day 5, 6 and 7)
Compar. 2	Predose Day 5 compared to (mean predose of Day 6 and 7)
Compar. 3	Predose Day 6 compared to predose Day 7 (0-hour)

The above statistical analyses were done using the SAS® Mixed procedure.

Formula

The following formulae in Table 18 were used for the ratio of least-squares means and 90% confidence interval calculations derived from the ANOVA on the ln transformed pharmacokinetic parameters.

TABLE 18

Ratio of Least-squares Means:	$100\times e^{(LSM_{Day7}-LSM_{Day1})}$

TABLE 18-continued

90% Confidence Interval:	$100 \times e^{(LSM_{Day7} - LSM_{Day1} \pm t_{df,0.05} \times SE_{Day7-Day1})}$

Note:

LSM_{Day7} and LSM_{Day1} are the least-squares means of Day 7 and Day 1, as computed by the LSMEANS statement of the SAS ® GLM procedure.

$t_{df,\alpha}$ is the value of the Student's t distribution with df degrees of freedom (i.e. degrees of freedom for the error term from the analysis of variance) and a right-tail fractional area of α ($\alpha = 0.05$).

$SE_{Day7-Day1}$ is the standard error of the difference between the adjusted Day means, as computed by the ESTIMATE statement in the SAS ® GLM procedure.

Discussion of Pharmacokinetic Results

Time Dependence Pharmacokinetic Linearity

The ANOVA model included Group, Day (1 (AUC_{inf}) and 7 (AUCτ)) and the interaction Day*Group as the fixed effect. All the interaction terms were not statistically significant, at a level of 5%, and were dropped from the final model. Pharmacokinetic linearity was calculated for the formulation using the same approach as above, but the ANOVA model included Group, Day 1 (AUCinf) and Day 7 (AUCτ)) and the interactions Group*Day as fixed effects and Subject nested within Group as a random effect.

The pharmacokinetic linearity results are summarized in the table below.

TABLE 19

		90% Confidence Interval	
Formulation	Ratio AUCτ/AUCinf	Lower Limit	Upper Limit
MR	97.3	86.5	109.5

The pharmacokinetic linearity results indicate that the ratios of least-squares means of AUCτ (Day 7) to AUC_{inf} (Day 1) and the 90% confidence interval for the MR formulation were within the 80-125% acceptance range. Based on these results, the 650 mg tranexamic acid modified release tablets exhibited linear pharmacokinetics following repeated administration (7 days) of a 1.3 g dose under fasting conditions.

Steady-State Analysis

For the steady-state analysis, the CS variance-covariance matrix was chosen to model the correlations within every subject. Overall, the interaction term (i.e. Time*Group) was not statistically significant and was removed from the final ANOVA model. For each formulation, the same approach as above was used, but the ANOVA models included Group, Time and the interactions Time*Group as fixed effects.

A summary of LSM results for the steady-state analysis are summarized in Table 20A below.

TABLE 20A

Formulation	Days	Times (hour)	LSM derived from the ANOVA
MR	4	-72	4.90536
	5	-48	4.77323
	6	-24	5.23678
	7	0	5.15389

Summary of statistical comparisons for the steady-state analysis are summarized in Table 20B below

TABLE 20B

Formulation	Helmert's contrasts	P-value
MR	Predose Day 4 compared to (mean predose of Day 5, 6 and 7)	0.4438
	Predose Day 5 compared to (mean predose of Day 6 and 7)	0.0393
	Predose Day 6 compared to predose Day 7	0.7318

Based on the results above, steady-state plasma concentration of tranexamic acid were reached on Day 4 (-72-hour), since the p value for the first contrast was not statistically significant at a 5% alpha error. It should be noted that the second comparison [Predose Day 5 compared to (mean of Day 6 and 7)] was found to be statistically significant.

The largest difference observed in predose plasma concentrations of tranexamic acid between the LSM of predose Day 5 compared to Day 6 and 7 was less than 10%, which is not considered clinically relevant. Moreover, the last contrast was not statistically significant and the observed difference between the LSM of predose Day 6 and 7 was less than 2%.

Compartmental Pharmacokinetic Analysis

The mean apparent oral clearance (CL/F) of the MR formulation calculated with compartmental methods was 17.7 L/h (295 mL/min). Based on previous data reported in the literature, the group of Pilbrant, et al., have determined that the urinary recovery of tranexamic acid exceeded 95% of the dose administered. Considering the bioavailability of the MR formulation (Mean F: 44.9%, See Table 5), the systemic clearance (CL) of tranexamic acid (295 mL/min×0.449=123 mL/min) would be close to the glomerilar filtration rate in healthy subjects (125 mL/min)5.

Using compartmental methods, the mean T½γ for the MR formulation was 16.6 hours. Similar values of terminal elimination half-life were previously reported in the literature. Pilbrant A., et al., *Eur. J. Clin. Pharmacol* (1981), 20: 65-72.

Following a single oral dose of 1.3 g of the MR formulation, the mean plasma concentrations of tranexamic acid observed at 28, 32, and 36 hours were 0.19724, 0.15672, and 0.13624 mcg/mL, respectively. Considering the therapeutic window of tranexamic acid (5-15 mcg/mL) and the very low plasma concentration levels observed at these timepoints, the terminal elimination half-life (T½γ) characterizing the slow decline of plasma concentrations should not play a clinically significant role in the frequency of drug administration.

Pharmacokinetic Conclusions

The pharmacokinetic linearity results indicate that the ratios of least-squares means of AUCτ (Day 7) to AUCinf (Day 1) and the 90% confidence interval for the MR formulation were within the 80-125% acceptance range. Based on these results, the 650 mg tranexamic acid modified release tablets exhibited linear pharmacokinetics following repeated administration (7 days) of a 1.3 g dose under fasting conditions.

Steady-state plasma concentrations of tranexamic acid for the modified-release tablets were reached on Day 4 (-72-hour), since the p-value for the first contrast was not statistically significant at a 5% alpha error

The pharmacokinetics of tranexamic acid was properly described using a three compartment PK model with linear elimination. The absorption kinetic of the single-dose (Day 1) data of tranexamic acid for the MR formulation was best described using a mixed-order rate constant of absorption.

Plasma Pharmacokinetic Parameters for the modified release (MR) formulation of Tranexamic Acid on day 1 are listed in Table 21 below.

TABLE 21

	ln AUC_{0-t}* (mcg · h/ml)	ln AUC_{inf}* (mcg · h/ml)	ln C_{max}* (mcg/ml)	T_{max} (h)	Half-life (h)	K_{el} (l/h)
Mean	74.571	76.875	13.176041	3.079	11.078	0.06443
CV %	31.3	30.4	33.1	25.0	16.9	18.3
N	19	19	19	19	19	19

*For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported; AUC_{0-t} = AUC post dose (0-36 hours)

Plasma Pharmacokinetic Parameters for the modified release (MR) formulation of Tranexamic Acid on day 7 are listed in Table 22 below.

TABLE 22

	ln AUC_τ* (mcg · h/ml)	ln C_{max}* (mcg/mL)	ln C_{min}* (mcg/ml)	T_{max} (h)	Flux 1** (%)	Flux 2** (%)
Mean	74.791	15.803509	5.157681	2.553	113.16	219.21
CV %	29.0	30.1	31.2	14.4	21.6	44.6
N	19	19	19	19	19	19

*For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported; AUC_τ = AUC dosing interval (8 hours)
**Defined in Table 16

Menorrhagia Instrument

In clinical trials the primary goal is to obtain definitive evidence regarding the benefit to risk profile of the pharmacotherapy. One of the most challenging design tasks in studies of heavy menstrual bleeding which is a subjective complaint is the choice of efficacy endpoints or outcome measures. The Applicants have established two criteria for assessing the clinical relevance of the reduction in menstrual blood loss in the clinical efficacy studies. The first criterion was that the mean reduction in menstrual blood loss should be greater than 50 mL. The second criterion was based on the correlation between the reduction in menstrual blood loss and the subjects' perception of a meaningful symptomatic change, derived from blinded data from the measures of the Menorrhagia Instrument (MI) in the first treated menstrual period in the menstrual cycle during a controlled clinical study for safety and efficacy of tranexamic acid in heavy menstrual Bleeding. Analysis of the data for the symptomatic measures of the Menorrhagia Instrument (MI, measure six, FIG. 7) established that a menstrual blood loss reduction of at least 36 mL as defined by the alkaline hematin test was regarded as meaningful by the clinical patients. The mean reduction in menstrual blood loss in patients treated with a tranexamic acid formulation at 1.9 and at 3.9 g/day met both criteria for a clinically meaningful result. Data from Menorrhagia Instrument (MI, measure six, FIG. 1, which establishes that the treatment was meaningful to the patient provides the treating practitioner with an assessment of patient response to tranexamic acid therapy.

Example 7

Mennoraghia Impact Measure Validation

Objective measurements of menstrual blood loss are not practical in the healthcare setting, and they correlate poorly with a woman's subjective assessment of blood loss and its simpact on quality of life [Warner 2004; National Collaborating Centre for Women's and Children's Health, 2007]. Menorrhagia is a subjective condition and may be practically defined as menstrual loss that is greater than the woman feels that she can reasonably manage. The amelioration of symptoms of heavy menstrual loss are practical efficacy benefits of the treatment are therefore important to measure and validate in a controlled clinical environment.

The MI was evaluated in a sub population of patients enrolled in a clinical trial designed to assess the safety and efficacy of modified release tranexamic acid formulations (Example 1) at an oral dose of 3.9 g administered daily for up to 5 days during each menstrual period. Two groups of patients were used to assess the MI, one group of patients were those diagnosed with menorrhagia and undergoing treatment. The second group was an age matched normal group. The sub-study was designed: to collect sufficient quantitative data to support the construct-related validation of the MI measures; to collect sufficient quantitative data to support the assessment of meaningful/important change in blood loss to the women; to conduct a test/retest evaluation of the instrument, and to address the reliability of the MI measures.

Study Methods

Development of the MI began with a review of the literature focusing on the methods used to collect qualitative data from menorrhagia patients. Qualitative interviews with patients determined which symptomatic concepts were most important to women and could be included in a draft Impact Measure. Cognitive debriefing interviews to evaluate patient understanding of items led to the synthesis of a patient-based instrument for assessing the impact of limitations caused by heavy menstrual bleeding. Published measures were used in the evaluation of the psychometric properties of the Menorrhagia Instrument to assess Construct-Related Validity. The reference measures include, the Ruta Menorrhagia Questionnaire [Ruta 1995] and the Medical Outcomes Study Short-Form 36 Item Health Status Instrument (SF-36) [Ware 1992]. Scoring of the standardized measures followed published algorithms, Table 23.

TABLE 23

Descriptions of Instruments used in this study

Measure	Score Generated	Score Ranges
Menorrhagia Impact Measure (MI)	Blood Loss Severity (Q1)	1 (light) thru 4 (very heavy)
	Limitation	
	Work outside or inside the home (Q2)	1 (not at all) thru 5 (extremely)
	Physical activities (Q3)	1 (not at all) thru 5 (extremely)
	Social or leisure activities (Q4)	1 (not at all) thru 5 (extremely)
	Activity list (Q5)	[Descriptive]
	Change in blood loss (follow-up) (Q6, 6a, 6b)	[15-pt scale: 0 = no change, 1-7 improve, 1-7 worse]
	Meaningful/important change (Q6c)	Y/N
Ruta Menorrhagia Questionnaire	Global	0 (asymptomatic)-42 (severe)
	Specific	
	Physical Function: Impact on work and daily activities (Q9 and Q10)	0 (asymptomatic)-6 (severe)
	Social Function: Impact on social and leisure activities and sex-life (Q11 and Q12)	0 (asymptomatic)-8 (severe)
SF-36	Physical Functioning, Role-Physical, Bodily Pain	0-100 (100 = minimal impairment)
	General Health (can be combined to form Physical Health Component Score); Vitality, Social Functioning, Role-Emotional, Mental Health (can be combined to form Mental Health Component Score)	

Study Design

A total of 262 women completed the MI. The MI measures 1 through 5 were administered after subject's baseline period

and after the subsequent first, second, third and sixth treatment periods. The MI measure 6 was administered after the first treatment period only. For this validation study, only the data collected through Month 1 of treatment was included in the analyses for the treatment cohort. The MI measures 1-5 were administered at baseline and at the subsequent first and second non-treatment periods for the subjects in the normal cohort The MI measure 6 was administered and data collected, at Month 1 and Month 2. The Ruta Menorrhagia Questionnaire, SF-36 Health Survey and the MIQ were completed by the subject before visit procedures were performed. A subset of at least 50 subjects were asked to return to the study site 7 to 10 days after the baseline Visit but before the next menstrual period starts to complete the MI a second time.

Treatment Group

A total of 177 patients were enrolled into the sub-study. During this time period 28 patients withdrew consent, dropped-out, or did not properly complete MI and were non-evaluable. The 149 patients remaining were intended to be age matched. The majority of patients in the study were in their late 30's or early 40's. Because of the difficulty of enrolling sufficient numbers of women with normal menstrual periods in this age bracket 18 evaluable patients were not age matched. A total of 131 evaluable patients were age matched. A sub-set of 80 evaluable patients participated in the test/retest segment of the validation. Of these patients 11 were evaluable but not age matched. Data from all 80 patients were used for statistical evaluation of the test/re-test correlations.

Normal Group

A group of women with self reported normal menstrual bleeding comprised the pool of normal women eligible for age matching in the study. A normal was defined as all of the following: a menstrual cycle between 26 and 32 days long, and their last (most recently completed) menstrual period was seven days or less in duration, the heaviest bleeding was three days or less, and the woman classified the bleeding overall as "light" or "moderate" as opposed to "heavy" or "very heavy. Women with normal periods who were enrolled into the study served as age-match controls for women recruited into the treatment group. Un-matching and re-matching occurred throughout the enrollment period if participants in either group dropped out of the study, if better re-matching increased the total number of matched pairs, or if the age-matched woman with normal periods did not enroll in the study.

Five women enrolled in the study did not complete the study through Visit 3. Another five women who did complete the study became 'unmatched' as the Treatment Group participant they had been matched to became non-evaluable. The 131 women who completed the study and remained matched are the Validation Sample Normal Group. A total of 51 women completed the Retest.

The following Measures were summarized and statistically analyzed:

- MI measure 1—Blood Loss Rating
- MI measure 2—Limitation of Work Outside or Inside the Home
- MI measure 3—Limitation of Physical Activities
- MI measure 4—Limitation of Social or Leisure Activities
- MI measure 6/6a/6b—Menstrual Blood Loss During Last Period
- MI measure 6c—Meaningfulness of Change in Menstrual Blood Loss

The statistics include the counts (missing data), mean, standard deviation, median, inter-quartile range, and minimum/maximum values. Differences in these variables between the treatment and normal cohorts were assessed using analysis of variance.

A p-value <0.05 was required for significance using two-sided hypothesis tests; no p-value adjustments were made for the analysis of multiple endpoints. All analyses were performed under SPSS version 11.5 for Windows, and the Stuart-Maxwell test for homogeneity was performed using Stata version 9.0 for Windows.

Validation of the MI was conducted using standardized analytic procedures found in the FDA Draft Guidance on Patient Reported Outcomes for Use in Evaluating Medical Products for Labeling Claims and instrument review criteria developed by the Scientific Advisory Committee of the Medical Outcomes Trust.[1]

1 Scientific Advisory Committee of the Medical Outcomes Trust. Assessing health status and quality-of-life instruments: attributes and review criteria. Qual Life Res. 2002; 11: 193-205

Evaluation of the Menorrhagia Instrument

The MI consisted of 4 individual measures (1-4) that were analyzed separately for validation. No summative scale was derived. Measure 5, served as descriptive of variables and did not undergo standard validation analyses. Measures 6, 6a and 6b dealt with menstrual blood loss relative to the previous menstrual period. The answers to the measures in the subparts of measure 6, were combined to produce a 15 point rating scale. The scale values range from −7 to +7 with −7 representing a very great deal worse menstrual blood loss than the previous period, and +7 representing a very great deal better menstrual blood loss than the previous period. The midpoint (0) represents the perception of about the same menstrual blood loss as the previous period.

Test-retest reliability assessed if items produced stable, reliable scores under similar conditions (Guttman, 1945). Reproducibility was evaluated in a subset of at least 50 from the treatment group and at least 50 from the normal group 7 to 10 days after the baseline visit using the intra-class correlation coefficient (ICC, see formula below). Values above 0.70 indicated the stability of an instrument over time. The following formula was used to compute the Intraclass Correlation Coefficient (ICC):

$$ICC = \frac{A^2 + B^2 + C^2}{A^2 + B^2 + D^2 - \left(\frac{C^2}{n}\right)}$$

where:

A = Standard deviation of baseline score

B = Standard deviation of Time 2 score

C = Standard deviation of change in score

D = mean of change in score

n = number of respondents

The data for each of the measures was above 0.70. In the test population, n=88, values of 0.72 (0.60-0.81), 0.75 (0.64-0.83), 0.77 (0.67-0.84) and 0.76 (0.66-0.84) for measures 1 to 4 respectively. The aged matched normal values where n=51 were 0.77 (0.63-0.86), 0.67 (0.49-0.80), 0.75 (0.60-0.85) and 0.86 (0.77-0.92) respectively.

Construct-Related Validity was established when relationships among items, domains, and concepts conform to what was predicted by the conceptual framework for the instrument. This includes convergent, discriminant, and known-groups validity. Convergent and discriminant validity was present where measures of the same construct are more highly related and measures of different constructs were less related. To assess convergent and discriminant validity, Pearson's correlation coefficients were computed between each MI measure and items and scales from the SF-36 and the Ruta Menorrhagia Questionnaire included in the study design and administered at the same visit. The following hypotheses were tested:

The MI Blood Loss Measure (#1) will have a stronger association with the Ruta Menorrhagia Questionnaire (RMQ) than to the SF-36 subscales.

The MI Physical Activity Limitation Measure (#3) will have a stronger association with the RMQ Physical Function scale, the SF-36 Physical domain, the SF-36 Role-Physical domain, and SF-36 Physical Component Summary score than the Ruta Social, SF-36 Social, and SF-36 Vitality domains.

The MI Social/Leisure Activity Limitation will have a have stronger associations with the RMQ Social Function scale and the SF-36 Social Function domain than the RMQ Physical, the SF-36 Physical and SF-36 Bodily Pain domains.

For convergent validity, the correlations of MI measures with Ruta subscales, SF-36 subscales, and diary data are shown in Table 24. The Ruta global score was highly correlated with each MI measures (range 0.757-0.809). The correlations of items with the SF-36 subscales were low to moderate, which is to be expected since the SF-36 is not a disease-specific measure, but rather a more generic health status measure unable to detect differences between a normal population and a population of women with menorrhagia. The MI measures were more strongly correlated with the SF-36 Physical and Role Physical subscales than other SF-36 subscales.

TABLE 24

Correlations Between Menorrhagia Instrument Patient Reported Outcome (PRO) Measures and Ruta/SF-36/Diary

	MI measure 1 Blood Loss	MI measure 2 Limit work outside or inside home	MI measure 3 Limit physical activity	MI measure 4 Limit social or leisure activity
Ruta - Global	0.767 (0.000)	0.785 (0.000)	0.807 (0.000)	0.809 (0.000)
Ruta - Physical Fx	0.512 (0.000)	0.682 (0.000)	0.646 (0.000)	0.664 (0.000)
Ruta - Social Fx	0.606 (0.000)	0.634 (0.000)	0.659 (0.000)	0.683 (0.000)
SF-36 - Physical Fx	−0.229 (0.000)	−0.234 (0.000)	−0.264 (0.000)	−0.273 (0.000)
SF-36 - Social Fx	−0.118 (0.057)	−0.194 (0.002)	−0.200 (0.001)	−0.261 (0.000)
SF-36 - Role Physical	−0.200 (0.001)	−0.279 (0.000)	−0.258 (0.000)	−0.303 (0.000)
SF-36 - Vitality	−0.143 (0.021)	−0.193 (0.002)	−0.248 (0.000)	−0.250 (0.000)
SF-36 - Bodily Pain	−0.087 (0.163)	−0.168 (0.006)	−0.192 (0.002)	−0.205 (0.001)
SF-36 - PCS	−0.190 (0.002)	−0.271 (0.000)	−0.285 (0.000)	−0.275 (0.000)

The data supported the hypothesis that the MI Blood Loss measure (#1) had a stronger association with the Ruta global score than to the SF-36 subscales. While the hypothesis that MI measure #3 (Physical Activity Limitation) would be strongly associated to the physical domains of the RMQ (r=0.65) and SF-36 (r=−0.26) was confirmed, this measure was also strongly correlated to the RMQ Social Functioning (r=0.66). MI measure #4 (Social or Leisure Activity Limitation) was highly correlated to the RMQ Social (r=0.68) and moderately associated with the SF-36 Social Functioning domain.

Known-groups validity determined the ability of the instrument to discriminate between groups of subjects known to be distinct. The ability of the MI items to discriminate among known groups was assessed by comparing the 4 items (1 thru 4) to responses from the two groups (treatment and normal) at baseline. Differences in these variables, between the treatment and normal groups, were assessed using analysis of variance. A p-value <0.05 was required for significance using two-sided hypothesis tests; no p-value adjustments was made for the analysis of multiple endpoints.

For each MI measure, the mean score for the treatment group was significantly different than the mean score for the normal group (p<0.001). The treatment group scores were higher for each individual measure, indicating greater limitation as a result of their excessive menstrual blood loss (see Table 25).

TABLE 25

Known-Groups Validity of the MIQ

		Treatment Cohort			AGE MATCH NORMAL Cohort			
		N	Mean	St. Dev.	N	Mean	St. Dev.	F (sig.)[1]
MI measure 1	Self-perceived blood loss	131	3.25	0.61	131	2.10	0.61	234.727 (<0.001)
MI measure 2	Limit you in your work	131	3.04	0.99	131	1.34	0.59	286.864 (<0.001)
MI measure 3	Limit you in your physical activities	131	3.28	0.95	131	1.49	0.72	299.011 (<0.001)
MI	Limit you in your	131	3.05	1.06	131	1.37	0.72	227.312

TABLE 25-continued

Known-Groups Validity of the MIQ

		Treatment Cohort			AGE MATCH NORMAL Cohort			
		N	Mean	St. Dev.	N	Mean	St. Dev.	F (sig.)[1]
measure 4	social/leisure activities							(<0.001)

The ability to detect change required that values for the item or instrument change when the concept it measures changed. In order to measure the MI items ability to detect change, longitudinal data were evaluated focusing primarily on the changes from baseline to month 1. Differences in proportions and comparisons between treatment and normal groups were compared using chi-square statistics (the Stuart-Maxwell test testing marginal homogeneity for all categories simultaneously). Cohen Effect Size statistics were also compared between the treatment and normal groups. The Cohen Effect Size was computed by taking the mean change in measure score (baseline to month 1) and dividing that by the standard deviation of mean baseline score[2].

2 Cohen, J. J. (1988). Statistical power analysis for the behavioral sciences (p. 8). Erlbaum: Hillsdale, N.J.

Ability to detect change was described for each item in Tables 26A-D by indicating the distribution of baseline and month 1 response option pairs for all patients. Change in responses from baseline to month 1 was tested using the Stuart-Maxwell test. For the treatment group, there was significant change in responses to each measure from baseline to month one ($p<0.001$). For the normal group, none of the items had significant changes in responses from baseline to month one. FIG. **8** illustrates the distribution of responses to measure 1 at baseline and at month one. In the treatment group, the proportion reporting light or moderate bleeding as measured with item 1, increased from baseline to month 1, and in the normal group this proportion changed very little.

TABLE 26A

Sensitivity to change of the MI Measure 1

Cohort		Response category	Month 1 Light	Moderate	Heavy	Very Heavy	Stuart-Maxwell test of association
Treatment	Baseline	Light	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	59.09 ($p < 0.001$)
		Moderate	0 (0.0%)	8 (6.3%)	4 (3.2%)	0 (0.0%)	
		Heavy	3 (2.4%)	41 (32.5%)	24 (19.0%)	2 (1.6%)	
		Very Heavy	2 (1.6%)	18 (14.3%)	13 (10.3%)	11 (8.7%)	
Normal	Baseline	Light	9 (6.9%)	5 (3.8%)	0 (0.0%)	0 (0.0%)	6.35 ($p = 0.130$)
		Moderate	12 (9.2%)	77 (59.2%)	4 (3.1%)	0 (0.0%)	
		Heavy	0 (0.0%)	9 (6.9%)	8 (6.2%)	2 (1.5%)	
		Very Heavy	0 (0.0%)	2 (1.5%)	2 (1.5%)	0 (0.0%)	

TABLE 26B

Sensitivity to change of the MI Measure 2

Cohort		Response category	Month 1 Not at all	Slightly	Moderately	Quite a bit	Extremely	Stuart-Maxwell test of association
Treatment	Baseline	Not at all	5 (4.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	53.33 ($p < 0.001$)
		Slightly	12 (9.5%)	11 (8.7%)	2 (1.6%)	1 (0.8%)	0 (0.0%)	
		Moderately	17 (13.5%)	26 (20.6%)	14 (11.1%)	1 (0.8%)	0 (0.0%)	
		Quite a bit	2 (1.6%)	8 (6.3%)	5 (4.0%)	9 (7.1%)	0 (0.0%)	

TABLE 26B-continued

Sensitivity to change of the MI Measure 2

			Month 1					
Cohort		Response category	Not at all	Slightly	Moderately	Quite a bit	Extremely	Stuart-Maxwell test of association
		Extremely	3 (2.4%)	3 (2.4%)	3 (2.4%)	1 (0.8%)	1 (0.8%)	
Normal	Baseline	Not at all	89 (69.0%)	5 (3.9%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	2.86 (p = 0.517)
		Slightly	8 (6.2%)	13 (10.1%)	4 (3.1%)	2 (1.6%)	0 (0.0%)	
		Moderately	0 (0.0%)	3 (2.3%)	4 (3.1%)	0 (0.0%)	0 (0.0%)	
		Quite a bit	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
		Extremely	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

TABLE 26C

Sensitivity to change of the MI Measure 3

			Month 1					Stuart-Maxwell
Cohort		Response category	Not at all	Slightly	Moderately	Quite a bit	Extremely	test of association
Treatment	Baseline	Not at all	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	64.58 (p < 0.001)
		Slightly	12 (9.5%)	21 (9.5%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	
		Moderately	14 (11.1%)	20 (15.9%)	11 (8.7%)	3 (2.4%)	0 (0.0%)	
		Quite a bit	6 (4.8%)	17 (13.5%)	9 (7.1%)	5 (4.0%)	0 (0.0%)	
		Extremely	5 (4.0%)	2 (1.6%)	2 (1.6%)	3 (2.4%)	2 (1.6%)	
Normal	Baseline	Not at all	72 (55.4%)	9 (6.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.99 (p = 0.708)
		Slightly	14 (10.8%)	18 (13.8%)	3 (2.3%)	1 (0.8%)	0 (0.0%)	
		Moderately	0 (0.0%)	6 (4.6%)	4 (3.1%)	1 (0.8%)	0 (0.0%)	
		Quite a bit	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	
		Extremely	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

TABLE 26D

Sensitivity to change of the MI Measure 4

			Month 1					Stuart-Maxwell
Cohort		Response category	Not at all	Slightly	Moderately	Quite a bit	Extremely	test of association
Treatment	Baseline	Not at all	6 (4.8%)	3 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	60.77 (p < 0.001)
		Slightly	16 (12.7%)	10 (7.9%)	0 (0.0%)	2 (1.6%)	0 (0.0%)	
		Moderately	19 (15.1%)	14 (11.1%)	12 (9.5%)	2 (1.6%)	1 (0.8%)	
		Quite a bit	5 (4.0%)	14 (11.1%)	4 (3.2%)	6 (4.8%)	0 (0.0%)	
		Extremely	3 (2.4%)	4 (3.2%)	1 (0.8%)	3 (2.4%)	1 (0.8%)	

TABLE 26D-continued

Sensitivity to change of the MI Measure 4

Cohort		Response category	Month 1: Not at all	Slightly	Moderately	Quite a bit	Extremely	Stuart-Maxwell test of association
Normal	Baseline	Not at all	84 (64.6%)	11 (8.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.71 (p = 0.807)
		Slightly	10 (7.7%)	14 (10.8%)	2 (1.5%)	0 (0.0%)	0 (0.0%)	
		Moderately	0 (0.0%)	4 (3.1%)	2 (1.5%)	0 (0.0%)	0 (0.0%)	
		Quite a bit	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.5%)	0 (0.0%)	
		Extremely	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

The amount of change in each item from baseline to month 1 is shown in Table 27. For the treatment group, the mean change in response from baseline to month 1 ranged from −0.76 to −1.16 for the four items. The calculated effect size shows this amount of change for each item ranged from −0.9 to −1.2. For the normal group, the mean change in response from baseline to month 1 ranged from 0.03 to −0.12 for the four items. The effect size for each item ranged from 0.053 to −0.197. This analysis shows a large response in patients undergoing treatment and little to no response in normal women who have received no treatment. This instrument is capable of identifying the perceived improvement in menstrual blood loss.

"Heavy" (MI measure 1) and then, following treatment (month 1), indicated being "Moderate" or "Light". When the treatment group was analyzed using the first responder definition, 69 (90%) of the 77 responders reported improvement and 63 (91%) of these rated this improvement as "a meaningful change". Thirty-five (71%) of the 49 non-responders reported improvement and 35 (92%) rated their change as "a meaningful change".

When the treatment group was analyzed using the second responder definition, 57 (89%) of the 64 responders reported improvement, and 52 (91%) reported their change to be meaningful. Forty-seven (76%) of the 62 non-responders reported improvement, and 45 (90%) reported their change to

TABLE 27

Sensitivity to Change of MI Effect Size

	Menorrhagia Item	BASELINE n	BASELINE Mean	BASELINE St Dev	MONTH 1 n	MONTH 1 Mean	MONTH 1 St Dev	CHANGE n	CHANGE Mean	CHANGE St Dev	Effect Size[1]
Item 1	Self-perceived blood loss	126	3.25	0.62	126	2.49	0.73	126	−0.76	0.84	−1.226
Item 2	Limit you in your work	126	3.05	0.99	126	2.12	0.99	126	−0.93	1.13	−0.939
Item 3	Limit you in your physical activities	126	3.29	0.95	126	2.13	1.00	126	−1.16	1.17	−1.221
Item 4	Limit you in your social/leisure activities	126	3.06	1.06	126	2.00	1.04	126	−1.06	1.19	−1.000

	Menorrhagia Item	BASELINE n	BASELINE Mean	BASELINE St Dev	CHANGE n	CHANGE Mean	n	Mean	St Dev	Effect Size
Item 1	Self-perceived blood loss	130	2.10	0.61	130	1.98	130	−0.12	0.56	−0.197
Item 2	Limit you in your work	129	1.32	0.57	129	1.35	129	0.03	0.50	0.053
Item 3	Limit you in your physical activities	130	1.49	0.72	130	1.43	130	−0.06	0.57	−0.083
Item 4	Limit you in your social/leisure activities	130	1.37	0.72	130	1.33	130	−0.04	0.58	−0.056

Responses from treatment group participants were divided based on two separate responder definitions. In the first definition, a responder was a patient indicating a one-category change in MI measure 1. In the second definition, a responder was a patient who entered the study as "Very heavy" or

be meaningful. Among the normal group, 96 (73%) of 130 patients reported no change. Twenty-one (16%) reported improvement, and 13 (10%) reported worsening. Of the patients reporting change, 15 (44%) rated the change as "a meaningful change".

For those women on treatment who reported a meaningful improvement (78.6%), MI items 3 and 4 showed the greatest treatment effect with improvements of 1.29 and 1.17, respectively. As expected, the majority of the Normal cohort (73.3%) reported no change in their menstrual period.

Example 8

The following clinical study was carried out in order to evaluate the efficacy and safety of tranexamic acid provided as an oral modified release formulation of Example 1 to reduce menstrual blood loss (MBL) in women with menorrhagia when administered during menstruation compared to placebo.

This was a multi-center, double-blind, placebo-controlled, parallel-group study. The study consisted of a screening phase of two (2) menstrual periods (no treatment) to determine eligibility, followed by a treatment phase spanning three (3) menstrual periods to assess the efficacy and safety of tranexamic acid during menstruation.

The primary objective of the study was to determine the efficacy of a 1.95 gm/day of tranexamic acid (650 mg orally three times daily, TID) and 3.9 gm/day of tranexamic acid (1.3 gm orally three times daily, TID) administered during menstruation for up to 5 days (maximum of 15 doses) to reduce menstrual blood loss in women with objective evidence of heavy menstrual bleeding.

The secondary objective of the study was to determine the improvement with administration of 1.95 gm/day or 3.9 gm/day of tranexamic acid in women with heavy menstrual bleeding in their symptoms including, Limitation in Social Leisure Activities (LSLA) and Limitation in Physical Activities (LPA) scores from the Menorrhagia Instrument Measures (FIG. 7). Further the objective was to determine the safety of the 1.95 gm/day and 3.9 gm/day of the modified release tranexamic acid formulation administered during menstruation.

Three treatment periods were averaged for the menstrual blood loss (MBL) primary efficacy evaluation (first, second, and third periods on treatment). All periods were evaluated for the secondary endpoints, and for safety of tranexamic acid at an oral dose of 1.3 gm or placebo administered three (3) times daily for up to five consecutive (5) days (maximum of 15 doses) during menstruation.

Criteria for Evaluation (Safety and Efficacy Assessments):

Efficacy Assessment

Menstrual blood loss (MBL) was assessed during the entire menstrual period by the alkaline hematin test (AHT) method. The Menorrhagia Instrument Measures (FIG. 7) were also administered immediately after each menstrual period under investigation. For the Primary Endpoint, the objective reduction in menstrual blood loss (MBL) during the entire menstrual period as assessed by the AHT Method was assessed.

For the Secondary Endpoints, the scores for Limitation in Social Leisure Activities (LSLA) and the scores for Limitation in Physical Activities (LPA) from the Menorrhagia Instrument Measures (MI), measures #4 and #3, respectively) were assessed.

For the Secondary Endpoints the data collected included at least; Menstrual Blood Loss (MBL) assessment score (MI measure 1), Limitation in Work Outside or Inside the Home (LWH) score (MI item 2), and subject assessment of meaningfulness score from the MI (measure 6) (used for the MBL responder analysis).

Efficacy Results

The efficacy results were based on the modified ITT (mITT) populations. Results from the analysis of other populations were very similar to those derived from the analysis of the mITT population, and do not alter the general conclusions presented below. The numbers of subjects in the mITT populations in the efficacy study are summarized in Table 28 below:

TABLE 28

Numbers of Subjects in mITT Populations in Pivotal Efficacy Studies

Treatment	N
Placebo	67
Tranexamic acid (1.95 g/day)	115
Tranexamic acid (3.9 g/day)	112

Primary Efficacy Endpoint

Subjects in both treatment groups experienced a significant reduction from baseline in mean MBL The mean reduction in MBL in subjects treated with the higher dose (3.9 g/day) was 65.3 mL, or 38.6% compared with the baseline value ($p<0.0001$). A smaller reduction was observed in subjects at the lower dose of 1.95 g/day (46.5 mL, 26.1%, $p<0.0001$). The reductions in both groups were statistically significant ($p<0.0001$) when compared with that in the placebo control group (2.98 mL).

Key Secondary Efficacy Endpoints

Significant treatment-related reductions from baseline in mean LSLA score and mean LPA score were observed. Other secondary efficacy endpoints provided supportive evidence of the efficacy of tranexainic acid. Specifically, subjects' assessments of MBL (MI item 1) and LWH (MI measure 2), were both significantly reduced for subjects in the 3.9 g/day tranexamic acid group compared with placebo. The number of patients responding to treatment was assessed. A responder was defined as a subject with a reduction in MBL and a subjective "meaningful" improvement according to the MI (measure 6c) after the first menstrual cycle during the treatment period. The proportion of responders in this study was 58.3% and 71.0% in the 1.95 and 3.9 g/day tranexamic acid groups respectively, compared with placebo response rate of 23.4% ($p<0.0001$ for both dose levels).

These results demonstrate that tranexamic acid at doses of 1.9 and 3.9 g/day ameliorates the symptoms associated with HMB, including at least limitations in social, leisure, and physical functioning. In addition, these results provide converging evidence that tranexamic acid modified-release tablets are efficacious in the treatment of HMB.

Heavy Menstrual Bleeding in Patients with Fibroids Included in Clinical Study of this Example

Analyses was initiated to assess tranexaminc acid modified release tablets treatment effect stratified by the presence of fibroids at baseline. The primary goal of this analysis was to evaluate treatment-by-fibroids effect across variety of endpoints. The results of the analysis is found in the following Tables:

TABLE 29.1

Treatment-Induced Changes in MBL (mL) over Three Cycles of Therapy
Stratified by the Presence of Fibroids
MITT Population

		Baseline MBL (mL)		Change in MBL from Baseline (mL)		Percent Change in MBL from Baseline (mL)	
Treatment	Statistics	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids
Tranexamic acid 3.9	N Mean (SD)	50	64	49	63	49	63
	Median	192 (93)	149 (68)	−80 (57)	−54 (43)	−41 (18)	−38 (25)
		172	129	−67	−51	−37	−43
Tranexamic acid 1.95	N Mean (SD)	44	72	44	71	44	71
	Median	211 (151)	157 (73)	−45 (69)	−47 (49)	−22 (31)	−27 (23)
		157	126	−38	−43	−26	−31
Placebo	N Mean (SD)	24	43	24	43	24	43
	Median	180 (93)	139 (43)	−5 (66)	−2 (31)	+2 (25)	0 (25)
		147	128	0	−2	0	−1

NOTE:
MEAN values for baseline cycles and in-treatment cycles are used in these calculations

TABLE 29.2

Treatment-Induced Changes in MBL (mL) over Three Cycles of Therapy
Stratified by the Presence of Fibroids
MITT Population

		Baseline MBL (mL)		Change in MBL from Baseline (mL)		Percent Change in MBL from Baseline (mL)	
Treatment	Statistics	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids
Tranexamic acid 3.9	N Mean (SD)	50	64	142	179	142	179
	Median	192 (93)	149 (68)	−79 (59)	−54 (49)	−41 (21)	−38 (29)
		172	129	−68	−55	−41	−43
Tranexamic acid 1.95	N Mean (SD)	44	72	125	209	125	209
	Median	211 (151)	157 (73)	−50 (79)	−48 (56)	−25 (34)	−27 (30)
		157	126	−45	−45	−29	−33
Placebo	N Mean (SD)	24	43	70	124	70	124
	Median	180 (93)	139 (43)	−1 (74)	−3 (42)	+3 (34)	−1 (32)
		147	128	+3	0	+1	0

NOTE:
MEAN baseline values are compared to the individual in-treatment cycles

TABLE 29.3

Percent of Subjects Reaching Specified MBL Reduction Targets over
Three Cycles of Therapy Stratified by the Presence of Fibroids
MITT Population

		Percent of subjects with >36 mL reduction in MBL		Percent of subjects with >50 mL reduction in MBL		Percent of subjects reaching normal range (<=80 mL)	
Treatment	Statistics	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids
Tranexamic acid 3.9	n/N (%)	45/53 (84.9%)	48/67 (71.6%)	35/53 (66.0%)	37/67 (55.2%)	20/53 (37.7%)	39/67 (58.2%)*
Tranexamic acid 1.95	n/N (%)	24/45 (53.3%)	41/73 (56.2%)	19/45 (42.2%)	30/73 (41.1%)	9/45 (20.0%)	24/73 (32.9%)
Placebo	n/N (%)	1/24 (4.2%)	8/45 (17.8%)	1/24 (4.2%)	5/45 (11.1%)	4/24 (16.7%)	8/45 (17.8%)

NOTE:
MEAN values for baseline cycles and in-treatment cycles are used in these calculations

TABLE 29.4

Percent of Subjects Reaching Specified MBL Reduction Targets for All Cycles of Therapy Stratified by the Presence of Fibroids MITT Population

		Percent of subjects with >36 mL reduction in MBL			Percent of subjects with >50 mL reduction in MBL			Percent of subjects reaching normal range (<=80 mL)		
Treatment	Statistics	With Fibroids	Without Fibroids	Total	With Fibroids	Without Fibroids	Total	With Fibroids	Without Fibroids	Total
Tranexamic acid 3.9	n/N	115/147	129/189	244/336	94/147	105/189	199/336	59/147	106/189	165/336
	(%)	(78.2%)	(68.3%)	(72.6%)	(64.0%)	(55.6%)	(59.2%)	(40.1%)	(56.1%)	(49.1%)
Tranexamic acid 1.95	n/N	81/132	127/213	208/345	65/132	91/213	156/345	37/132	79/213	116/345
	(%)	(61.4%)	(59.6%)	(60.3%)	(49.2%)	(42.7%)	(45.2%)	(28.0%)	(37.1%)	(33.6%)
Placebo	n/N	13/75	29/129	42/201	10/72	21/129	31/201	13/72	36/129	39/201
	(%)	(18.1%)	(22.5%)	(20.9%)	(13.9%)	(16.3%)	(15.4%)	(18.1%)	(20.2%)	(19.4%)

NOTE:

MEAN baseline values are compared to the individual in-treatment cycles

TABLE 30

Treatment-Induced Changes in MI Q1 over Three Cycles of Therapy Stratified by the Presence of Fibroids MITT Population

		Baseline Q1		Post-Baseline Q1		Change in Q1 from Baseline	
Treatment	Statistics	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids
Tranexamic acid 3.9	N Mean (SD)	49	63	49	63	49	63
	Median	2.92 (0.61)	2.71 (0.63)	2.27 (0.57)	2.19 (0.71)	−0.65 (0.70)	−0.53 (0.80)
		3.0	2.5	2.33	2.0	−0.67	−0.5
Tranexamic acid 1.95	N Mean (SD)	44	71	44	71	44	71
	Median	2.80 (0.63)	2.82 (0.56)	2.40 (0.67)	2.39 (0.62)	−0.39 (0.60)	−42 (0.65)
		3.0	3.0	2.33	2.33	−0.33	−0.5
Placebo	N Mean (SD)	24	42	24	42	24	42
	Median	2.85 (0.52)	2.79 (0.61)	2.67 (0.54)	2.74 (0.53)	−0.18 (0.53)	−0.05 (0.84)
		3.0	3.0	2.67	2.67	+0.25	0.0

TABLE 30.1

Treatment-Induced Changes in MI Q2 over Three Cycles of Therapy Stratified by the Presence of Fibroids MITT Population

		Baseline Q2		Post-Baseline Q2		Change in Q2 from Baseline	
Treatment	Statistics	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids
Tranexamic acid 3.9	N Mean (SD)	49	63	49	63	49	63
	Median	3.15 (0.90)	2.99 (1.01)	2.17 (0.94)	2.07 (0.96)	−0.99 (0.87)	−0.92 (1.08)
		3.0	3.0	2.0	2.0	−1.0	−0.83
Tranexamic acid 1.95	N Mean (SD)	44	71	44	71	44	71
	Median	2.98 (1.05)	2.82 (0.56)	2.38 (0.86)	2.27 (0.94)	−0.59 (0.80)	−0.56 (0.97)
		3.0	3.0	2.33	2.33	−0.67	−0.67
Placebo	N Mean (SD)	24	42	24	42	24	42
	Median	2.98 (0.85)	2.69 (0.92)	2.78 (0.84)	2.49 (0.92)	−0.19 (0.85)	−0.20 (0.76)
		3.0	2.75	2.67	2.42	0.0	−0.17

TABLE 30.2

Treatment-Induced Changes in MI Q3 over Three Cycles of Therapy
Stratified by the Presence of Fibroids
MITT Population

		Baseline Q3		Post-Baseline Q3		Change in Q3 from Baseline	
Treatment	Statistics	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids
Tranexamic acid 3.9	N Mean (SD)	49	63	49	63	49	63
	Median	3.17 (1.06)	2.98 (1.02)	2.13 (0.93)	2.07 (0.96)	−1.05 (0.93)	−0.92 (1.10)
		3.0	3.0	20	2.0	−1.0	−0.67
Tranexamic acid 1.95	N Mean (SD)	44	71	44	71	44	71
	Median	2.92 (1.09)	3.01 (0.90)	2.36 (0.81)	2.24 (0.97)	−0.56 (0.80)	−0.77 (0.94)
		3.0	3.0	2.33	2.00	−0.58	−0.83
Placebo	N Mean (SD)	24	42	24	42	24	42
	Median	3.15 (0.88)	2.86 (0.85)	2.72 (0.90)	2.60 (0.90)	−0.42 (0.78)	−0.26 (0.81)
		3.0	3.0	2.67	2.67	−0.42	0.0

TABLE 30.3

Treatment-Induced Changes in MI Q4 over Three Cycles of Therapy
Stratified by the Presence of Fibroids
MITT Population

		Baseline Q4		Post-Baseline Q4		Change in Q4 from Baseline	
Treatment	Statistics	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids	With Fibroids	Without Fibroids
Tranexamic acid 3.9	N Mean (SD)	49	63	49	63	49	63
	Median	3.08 (1.11)	2.93 (1.05)	2.00 (0.92)	1.97 (1.05)	−1.08 (1.10)	−0.96 (1.13)
		3.0	3.0	2.0	1.67	−1.0	−0.83
Tranexamic acid 1.95	N Mean (SD)	44	71	44	71	44	71
	Median	2.98 (1.05)	2.89 (0.97)	2.28 (0.82)	2.13 (0.94)	−0.70 (0.83)	−0.76 (0.98)
		3.0	3.0	2.33	2.00	−0.67	−0.83
Placebo	N Mean (SD)	24	42	24	42	24	42
	Median	3.06 (0.95)	2.73 (0.98)	2.68 (0.83)	2.40 (0.91)	−0.38 (0.83)	−0.32 (0.86)
		3.5	2.75	2.67	2.33	−0.33	−0.17

TABLE 30.5

Treatment-Induced Changes in MI Q6A-B at Cycle 1
Stratified by the Presence of Fibroids
MITT Population

		Change in Q6A-B from Baseline		
Treatment	Statistics	With Fibroids	Without Fibroids	Total
Tranexamic acid 3.9	N	46	59	105
	Mean (SD)	4.1 (2.4)	3.1 (3.5)	3.5 (3.1)
	Median	5.0	3.0	4.0
Tranexamic acid 1.95	N	42	67	109
	Mean (SD)	2.8 (2.4)	2.7 (3.2)	2.7 (2.9)
	Median	3.0	3.0	3.0
Placebo	N	24	40	64
	Mean (SD)	−0.3 (3.6)	0.8 (3.8)	0.4 (3.8)
	Median	0	0	0

NOTE:
MI items 6, 6a and 6b are combined into one scale ranging from −7 to +7. There are very strong reasons for this approach.

Example 9

The following clinical study was carried out in order to evaluate the efficacy and safety of the modified release (MR) oral formulation of tranexamic acid of Example 1 to reduce menstrual blood loss (MBL) in women with menorrhagia when administered during menstruation compared to placebo.

This was a multi-center, double-blind, placebo-controlled, parallel-group study. The study consisted of a screening phase of two (2) menstrual periods (no treatment) to determine eligibility, followed by a treatment phase spanning six (6) menstrual periods to assess the efficacy and safety of tranexamic acid during menstruation.

The primary objective of the study was to determine the efficacy of a 3.9 gm/day (1.3 gm orally three times daily, TID) administered during menstruation for up to 5 days (maximum of 15 doses) to reduce menstrual blood loss in women with objective evidence of heavy menstrual bleeding.

The secondary objective of the study included an evaluation of the improvement observed from 3.9 gm/day of the modified release tranexamic acid formulation administered during menstruation in women with heavy menstrual bleeding on Limitation in Social Leisure Activities (LSLA) (item 4) and Limitation in Physical Activities (LPA) (MI measure #3) scores from the Menorrhagia Instruments (FIG. 7). Four treatment periods were averaged for the menstrual blood loss (MBL) primary efficacy evaluation (first, second, third and sixth periods). All periods were evaluated for the secondary endpoints, the secondary endpoints, and for safety of tranexamic acid at an oral dose of 1.3 gm or placebo administered three (3) times daily for up to five consecutive (5) days (maximum of 15 doses) during menstruation.

Criteria for Evaluation

Menstrual blood loss (MBL) was assessed during the entire menstrual period by the alkaline hematin test (AHT) method.

Measures from the Menorrhagia Instrument (FIG. 7) were also administered immediately after each menstrual period under investigation. Subjects reported large stains exceeding the capacity of sanitary protection (and other patient reported outcome [PRO] items) during the menstrual period in daily diaries.

For the Primary Endpoint, the objective reduction in menstrual blood loss (MBL) during the entire menstrual period as assessed by the AHT Method was assessed.

For the Secondary Endpoints, the Limitation in Social Leisure Activities (LSLA) and the Limitation in Physical Activities (LPA) scores from the Menorrhagia Instrument (MI measures #4 and #3, respectively) and the total number of large stains responder analysis during the menstrual period from subject diaries were assessed.

For the Secondary Endpoints, assessment of the following were included, Menstrual Blood Loss (MBL) assessment score (MI measure #1), Limitation in Work Outside or Inside the Home (LWH) score (MI measure #2), and subject assessment of meaningfulness score from the MI (Measure #6) (used for the MBL responder analysis).

Efficacy Results

The efficacy results were based on the modified ITT (mITT) populations. The numbers of subjects in the mITT populations in the efficacy study are summarized in the Table below:

TABLE 31

Numbers of Subjects in mITT Populations in Pivotal Efficacy Studies

Treatment	N
Placebo	72
Tranexamic acid (3.9 g/day)	115

Primary Efficacy Endpoint

Subjects experienced a significant reduction from baseline in mean MBL. The mean reduction in MBL in the tranexamic acid-treated subjects was 69.6 mL, or 40.4% compared with the baseline value ($p<0.0001$). The reduction in MBL was also statistically significant ($p<0.0001$) when compared with that in the placebo control group (12.6 mL, 8.2%).

Secondary Efficacy Endpoints

For the secondary efficacy endpoints, significant treatment-related reductions from baseline in mean LSLA score and mean LPA score were observed. Subjects' assessments of MBL (MI measure #1) and LWH (MI measure #2), were both significantly reduced for subjects in the 3.9 g/day tranexamic acid group compared with placebo.

The number of patients responding to treatment was assessed as described in the previous example. A responder was defined as a subject with a reduction in MBL and a subjective "meaningful" improvement according to the MI (measure #6c) after the first menstrual cycle during the treatment period. The proportion of responders increased in the 3.9 g/day tranexamic acid treatment group (65.4%) compared with the placebo group (31.8%, $p<0.0001$). These results demonstrate that 3.9 g/day tranexamic acid ameliorates the symptoms associated with HMB, including improvement in limitations in social, leisure, and physical functioning. In addition, these results provide converging evidence that tranexamic acid modified-release tablets are efficacious in the treatment of HMB.

In both the Example 8 and Example 9 studies, the reduction in menstrual blood loss (MBL) was evident in the first menstrual period after commencing treatment with 3.9 g/day tranexamic acid. The response to treatment was maintained for the duration of the study (three and six menstrual cycles in Example 8 and Example 9 respectively; Regression analysis in the study of Example VIII confirmed that the response to tranexamic acid was durable over the six menstrual cycles (regression slope of −0.90 mL/cycle, p−0.615).

Summary of Clinical Findings from the Studies of Examples 8 and 9

The efficacy and safety of the tranexamic acid (TXA MR) modified release tablets in the treatment of HMB was demonstrated in one 3-cycle treatment and one 6-cycle treatment, randomized, double-blind, placebo-controlled study. In these studies, the primary outcome measure was menstrual blood loss (MBL), measured using a validated menstrual blood loss method. The key secondary outcome measures were based on responses to items on the Menorrhagia Instrument (MI), a validated disease-specific patient-reported outcome instrument that measured Limitations in Social or Leisure activities and Limitations in Physical Activities. Large stains (soiling beyond the undergarment) and sanitary product use were also included as secondary outcome measures. In these studies, subjects were 18 to 49 years of age with a mean age of approximately 40 years and a BMI of approximately 32 kg/m2. On average, subjects had an HMB history of approximately 10 years and 40% had fibroids as determined by transvaginal ultrasound. About 20% were smokers and approximately 50% reported using alcohol. Approximately 70% were Caucasian, 25% were Black, and 5% were Asian, Native American, Pacific Islander, or Other. Seven percent (7%) of subjects were of Hispanic origin. In addition, approximately 18% of subjects were taking multivitamins and 7% of subjects were taking iron supplements.

Three-Cycle Treatment Study

This study compared the effects of two doses of tranexamic acid modified release tablets (1.95 g and 3.9 g given daily for up to 5 days during each menstrual period) versus placebo on MBL over a 3-cycle treatment duration. A total of 304 patients (117 TXA MR 1.95 g/day, 118 TXA MR 3.9 g/day, 69 Placebo) were randomized. MBL was significantly reduced in patients treated with 3.9 g/day TXA MR compared to placebo (mean 3.9 g/day TXA MR=65.31 mL [percent MBL reduction=38.6%]; placebo mean=2.98 mL [percent MBL reduction=1.9%]; $p<0.0001$). This reduction met the criteria for being a clinically meaningful improvement (MBL≧50 mL) and a meaningful improvement to women who participated in the trial (MBL≧36 mL). The 1.95 g/day dose did not meet the clinically meaningful improvement criteria for efficacy thereby establishing 3.9 g/day TXA MR as the minimally effective dose.

Tranexamic acid modified release tablets also significantly reduced limitations on social, leisure, and physical activities as measured by questions on the MI, and sanitary products used in the 3.9 g/day dose group compared to placebo (see Table 32). No significant treatment differences were observed in response rates on the number of large stains.

TABLE 32

Secondary Outcomes in 3-Cycle Study

Outcome Measure	N	Mean (SD) Reduction*	P-value vs. Placebo
Social and Leisure Activities (MI)			
3.9 gm/day TXA MR	112	1.10 (1.12)	<0.0001
Placebo	66	0.34 (0.85)	
Physical Activities (MI)			
3.9 gm/day TXA MR	112	0.97 (1.03)	<0.0001
Placebo	66	0.32 (0.80)	
Sanitary Products Used			
3.9 gm/day TXA MR	112	6.36 (6.80)	<0.0001
Placebo	67	2.40 (6.13)	
Reduction in Large Stains**			
3.9 gm/day TXA MR	111	71 (64.0)	0.156
Placebo	67	35 (52.2)	

*Positive means reflect a decrease from baseline

**The reduction in large stains is reported as the number (%) of women who were classified as responders (i.e., subjects who experienced a positive change from baseline)

Six-Cycle Treatment Study

This study compared the effects of one dose of TXA MR (3.9 g/day) versus placebo on MBL over a 6-cycle treatment duration. A total of 196 patients (123 TXA MR 3.9 g/day, 73 Placebo) were randomized. Replicating the results from the 3-cycle treatment study, MBL was significantly reduced in patients treated with 3.9 g/day TXA MR compared to placebo (mean 3.9 g/day TXA MR=69.6 mL [percent MBL reduction=40.4%]; placebo mean=12.6 mL [percent MBL reduction=8.2%]; p<0.0001). This reduction met the criterion for being a clinically meaningful improvement (MBL≧50 mL) and a meaningful improvement to women (MBL≧36 mL). Limitations on social, leisure, and physical activities were also significantly reduced in the 3.9 g/day TXA MR dose group compared to placebo (see Table 33). No significant treatment differences were observed in sanitary products used or in response rates on the number of large stains.

TABLE 33

Secondary Outcomes in 6-Cycle Study

Outcome Measure	N	Mean (SD) Reduction*	P-value vs. Placebo
Social and Leisure Activities (MI)			
3.9 gm/day TXA MR	115	0.89 (0.85)	<0.0001
Placebo	72	0.38 (0.82)	
Physical Activities (MI)			
3.9 gm/day TXA MR	115	0.90 (0.86)	<0.0001
Placebo	72	0.35 (0.90)	
Sanitary Products Used			
3.9 gm/day TXA MR	115	5.20 (6.39)	0.129
Placebo	72	4.03 (5.94)	
Reduction in Large Stains**			
3.9 gm/day TXA MR	115	66 (57.4)	0.453
Placebo	72	37 (51.4)	

*Positive means reflect a decrease from baseline

**The reduction in large stains is reported as the number (%) of women who were classified as responders (i.e., subjects who experienced a positive change from baseline)

Example 10

Additional Pharmacokinetics

The pharmacokinetics of the modified release tranexamic acid tablets of Example 1 were further evaluated. After oral administration peak plasma levels (C_{max}) occurred at approximately 3 hours (T_{max}). The systemic bioavailability of the tablets in women aged 18-49 was approximately 45%. The mean C_{max} and the area under the plasma concentration curve (AUC) remained unchanged after repeated (1.3 gm TID) oral dosing for 5 days as compared to a single 1.3 gm oral dose.

The C_{max} and AUC after administration of a single 1.3 gm dose of tranexamic modified release tablets increased by 7% and 15% after food intake compared to fasting conditions, respectively. Therefore, the modified release tranexamic acid tablets can be taken with food.

The pharmacokinetic profile of the modified release tranexamic acid tablets was determined in 39 healthy women following a single 1.3 gm oral dose compared to repeated doses of 1.3 gm TID for 5 days. The results are shown in Table 34.

TABLE 34

Parameter	1 day	5 days
Dose	1.3 gm	1.3 gm TID[a]
AUC (mcg * h/L)	74.6[b]	74.8[c]
Coefficient of variation	33%	30%
C_{max} (mg/L)	13.2	15.8 (5.2[d])
T_{max} (h)	3.1	2.6
$T_{1/2}$ (h)[e]	11.1	N/A

Note:
Values represent geometric means, except Tmax which is the arithmetic mean.
[a]Dosed every 8 hours (3.9 g/day)
[b]AUC_{0-t}
[c]AUC_{τ}
[d]C_{min} corresponding steady-statie concentration
[e]Reflects terminal half-life

CONCLUSION

While the invention herein disclosed has been described by means of specific embodiments and applications thereof, numerous modifications and variations could be made thereto by those skilled in the art without departing from the spirit and scope of the present invention. Such modifications are understood to be within the scope of the appended claims.

In the preceding specification, the invention has been described with reference to specific exemplary embodiments and examples thereof. It will, however, be evident that various modifications and changes may be made thereto without departing from the broader spirit and scope of the invention as set forth in the claims that follow. The specification and drawings are accordingly to be regarded in an illustrative manner rather than a restrictive sense.

What is claimed is:

1. A tranexamic acid oral dosage form comprising:

tranexamic acid or a pharmaceutically acceptable salt thereof; and

a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis;

wherein the modified release material comprises a polymer selected from the group consisting of hydroxyalkylcelluloses, alkylcelluloses, cellulose ethers, partial esters thereof, and mixtures thereof;

wherein the modified release material is present in the formulation in an amount from about 10% to about 35% by weight of the formulation;

wherein said dosage form provides an in-vitro dissolution release rate of the tranexamic acid or pharmaceutically acceptable salt thereof, when measured by a USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C., of less than about 40% tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, less than about 70% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes and not less than about 50% by weight of said tranexamic acid or pharmaceutically acceptable salt thereof released by about 90 minutes; and

wherein each tranexamic acid oral dosage form provides a dose of about 650 mg of tranexamic acid.

2. The tranexamic acid oral dosage form of claim **1**, wherein said dosage form provides an in-vitro dissolution release rate of the tranexamic acid or pharmaceutically acceptable salt thereof, when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C., of about 0% to about 40% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, from about 20% to about 60% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 30 minutes, from about 40% to about 65% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, from about 50% to about 95% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 60 minutes, and not less than about 60% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes.

3. The tranexamic acid oral dosage form of claim **1**, wherein the dosage form releases about 10% to about 25% by weight tranexamic acid or pharmaceutically acceptable salt thereof every 15 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C.

4. The tranexamic acid oral dosage form of claim **1**, wherein the dosage form releases about 1% tranexamic acid or pharmaceutically acceptable salt thereof every minute when measured in-vitro utilizing the USP 27 Apparatus Type II paddle method at 50 RPM in 900 ml water at 37±0.5° C.

5. The tranexamic acid oral dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of tranexamic acid in a range from about 9 to about 14.5 mcg/ml after single dose oral administration of two of said tranexamic acid oral dosage forms to humans.

6. The tranexamic acid oral dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of tranexamic acid in a range from about 5 to about 25 mcg/ml after steady state oral administration of two of said tranexamic acid oral dosage forms to humans.

7. The tranexamic acid oral dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of tranexamic acid in a range from about 10 to about 20 mcg/ml after steady state oral administration three times daily of two of said tranexamic acid oral dosage forms to humans.

8. The tranexamic acid oral dosage form of claim **1**, which provides mean time to maximum plasma concentration (T_{max}) at a time in a range from about 1.0 to about 5.5 hours after oral administration of one or more of said tranexamic acid oral dosage forms to humans.

9. The tranexamic acid oral dosage form of claim **1**, wherein the dosage form provides a mean transit time of said tranexamic acid of 7.70±0.72 hours when orally administered across a patient population.

10. The tranexamic acid oral dosage form of claim **1**, wherein the dosage form provides a mean absorption time of said tranexamic acid of 4.18±0.70 hours when orally administered across a patient population.

11. The tranexamic acid oral dosage form of claim **1**, which provides for the reduction of at least one side effect selected from the group consisting of headache, nausea, vomiting, diarrhea, constipation, cramping, bloating, and combinations thereof, as compared to an immediate release oral dosage form containing an equivalent amount of tranexamic acid or pharmaceutically acceptable salt thereof, when administered across a same or different population of patients as said modified release dosage form, and wherein said immediate release dosage form releases all of said tranexamic acid or pharmaceutically acceptable salt thereof within about 45 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C.

12. The tranexamic acid oral dosage form of claim **1**, which provides a mean transit time of said tranexamic acid which is at least about 20 minutes longer than an immediate release formulation of tranexamic acid when administered across a patient population.

13. The tranexamic acid oral dosage form of claim **1**, which provides a mean absorption time of said tranexamic acid which is at least about 20 minutes longer than an immediate release formulation containing an equivalent amount of tranexamic acid or pharmaceutically acceptable salt thereof when administered across a patient population, wherein said immediate release dosage form releases all of said tranexamic acid or pharmaceutically acceptable salt thereof within about 45 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C.

14. The tranexamic acid oral dosage form of claim **1**, wherein said dosage form provides less headache, nausea, or combination thereof in comparison to a therapeutically equivalent amount of tranexamic acid or pharmaceutically acceptable salt thereof administered intravenously in five minutes or less when administered across a patient population.

15. The tranexamic acid oral dosage form of claim **1**, wherein said dosage form is selected from the group consisting of one or more tablets, capsules, granules, powders, pellets, dragees, troches, non-pareils, and pills.

16. The tranexamic acid oral dosage form of claim **1**, wherein said dosage form provides a bioavailability of said tranexamic acid of greater than 40% when administered to humans.

17. The tranexamic acid oral dosage form of claim **1**, wherein the dosage form is a matrix tablet which comprises a pre-granulated drug mixed together with the modified release material.

18. The tranexamic acid oral dosage form of claim 1, wherein the modified release material comprises a hydroxyalkylcellulose or a cellulose ether.

19. The tranexamic acid oral dosage form of claim 1, wherein the modified release material comprises hydroxypropylmethylcellulose.

20. The tranexamic acid oral dosage form of claim 1, wherein the modified release material is present in an amount of about 15% by weight of the formulation.

21. The tranexamic acid oral dosage form of claim 19, wherein the modified release material is present in an amount of about 15% by weight of the formulation.

22. The tranexamic acid oral dosage form of claim 19, wherein the hydroxypropylmethylcellulose is present in an amount of about 10% to about 35% by weight of the formulation.

23. The tranexamic acid oral dosage form of claim 22, wherein the hydroxypropylmethylcellulose is present in an amount of about 15% by weight of the formulation.

24. A tranexamic acid oral dosage form comprising:

tranexamic acid or a pharmaceutically acceptable salt thereof; and

hydroxypropylmethylcellulose in an amount from about 10% to about 35% by weight of the dosage form;

wherein the formulation provides an in-vitro dissolution release rate of the tranexamic acid or pharmaceutically acceptable salt thereof, when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. of less than about 40% tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, less than about 70% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, and not less than about 50% by weight tranexamic acid or pharmaceutically acceptable salt thereof released by about 90 minutes;

and

wherein each dosage form provides a dose of about 650 mg of tranexamic acid.

25. The tranexamic acid oral dosage form of claim 24, wherein the hydroxypropylmethylcellulose is present in an amount of about 15% by weight of the formulation.

26. The tranexamic acid oral dosage form of claim 24, wherein the tranexamic acid or pharmaceutically acceptable salt thereof, is present in an amount from about 60% to about 90% by weight of the formulation.

27. A tranexamic acid oral dosage form comprising:

tranexamic acid or a pharmaceutically acceptable salt thereof; and

hydroxypropylmethylcellulose in an amount from about 10% to about 35% by weight of the formulation;

wherein the formulation releases from about 10% to about 25% by weight tranexamic acid or pharmaceutically acceptable salt thereof every 15 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. such that not less than about 60% of the tranexamic acid or pharmaceutically acceptable salt thereof is released by about 90 minutes;

and

wherein the amount of tranexamic acid or pharmaceutically acceptable salt thereof included in the dosage form provides a dose of about 650 mg of tranexamic acid.

28. The tranexamic acid oral dosage form of claim 27, wherein the tranexamic acid or pharmaceutically acceptable salt thereof, is present in an amount from about 60% to about 90% by weight of the formulation.

29. The tranexamic acid oral dosage form of claim 27, wherein the hydroxypropylmethylcellulose is present in an amount of about 15% by weight of the dosage form.

30. A method of treating menorrhagia comprising administering to a human subject in need of such treatment a dosage form according to claim 1.

31. The method of claim 30, wherein the dosage form is administered three times daily.

32. The method of claim 30, wherein two dosage forms are administered three times daily.

33. The method of claim 30, comprising administering a single dose of about 1300 mg of tranexamic acid or pharmaceutically acceptable salt thereof.

34. The method of claim 33, comprising administering a single dose of about 1300 mg of tranexamic acid or pharmaceutically acceptable salt thereof three times daily.

35. The method of claim 30, wherein said dosage form is selected from the group consisting of one or more tablets, capsules, granules, powders, pellets, dragees, troches, nonpareils, and pills.

36. The method of claim 30, wherein the dosage form is a tablet.

37. The method of claim 30, wherein a mean maximum plasma concentration (C_{max}) of tranexamic acid in a range from about 10 to about 20 mcg/ml is provided after steady state oral administration three times daily of about 1300 mg of tranexamic acid or pharmaceutically acceptable salt thereof included in one or more of said modified release oral dosage form to humans.

38. The method of claim 30, which provides for the reduction of at least one side effect selected from the group consisting of headache, nausea, vomiting, diarrhea, constipation, cramping, bloating, and combinations thereof, as compared to an immediate release oral dosage form containing an equivalent amount of tranexamic acid or pharmaceutically acceptable salt thereof, when administered across a same or different population of patients as said modified release dosage form, and wherein said immediate release dosage form releases all of said tranexamic acid or pharmaceutically acceptable salt thereof within about 45 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C.

39. The method of claim 30, wherein the dosage form is a matrix tablet which comprises a pre-granulated drug mixed together with the modified release material.

40. The method of claim 30, wherein the modified release material comprises a hydroxyalkylcellulose or a cellulose ether.

41. The method of claim 30, wherein the modified release material comprises hydroxypropylmethylcellulose.

42. The method of claim 30, wherein the modified release material is present in an amount of about 15% by weight of the formulation.

43. The method of claim 30, wherein the modified release material is present in an amount of about 15% by weight of the formulation.

44. The method of claim 30, wherein the hydroxypropylmethylcellulose is present in an amount of about 10% to about 35% by weight of the formulation.

45. The method of claim 30, wherein the hydroxypropylmethylcellulose is present in an amount of about 15% by weight of the formulation.

46. A method of treating menorrhagia comprising administering to a human subject in need of such treatment a dosage form according to claim 24.

47. The method of claim 46, comprising administering a 1300 mg dose of tranexamic acid three times daily.

48. A method of treating menorrhagia comprising administering to a human subject in need of such treatment a dosage form according to claim 25.

49. The method of claim 48, comprising administering a 1300 mg dose of tranexamic acid three times daily.

50. A method of treating menorrhagia comprising administering to a human subject in need of such treatment a dosage form according to claim 26.

51. The method of claim **50**, comprising administering a 1300 mg dose of tranexamic acid three times daily.

52. A method of treating menorrhagia comprising administering to a human subject in need of such treatment a dosage form according to claim **27**.

53. The method of claim **52**, comprising administering a 1300 mg dose of tranexamic acid three times daily.

54. A method of treating menorrhagia comprising administering to a human subject in need of such treatment a dosage form according to claim **28**.

55. The method of claim **52**, comprising administering a 1300 mg dose of tranexamic acid three times daily.

56. A method of treating menorrhagia comprising administering to a human subject in need of such treatment a dosage form according to claim **29**.

57. The method of claim **52**, comprising administering a 1300 mg dose of tranexamic acid three times daily.

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February 28, 2013

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U.S. PATENT: *8,273,795*

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Trial Exhibit

(12) **United States Patent**
Moore et al.

(10) **Patent No.: US 8,273,795 B2**
(45) **Date of Patent: *Sep. 25, 2012**

(54) **TRANEXAMIC ACID FORMULATIONS**

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A61K 31/19 (2006.01)
A61K 31/195 (2006.01)

(52) **U.S. Cl.** **514/574**; 514/561

(58) **Field of Classification Search** 514/561, 514/574

See application file for complete search history.

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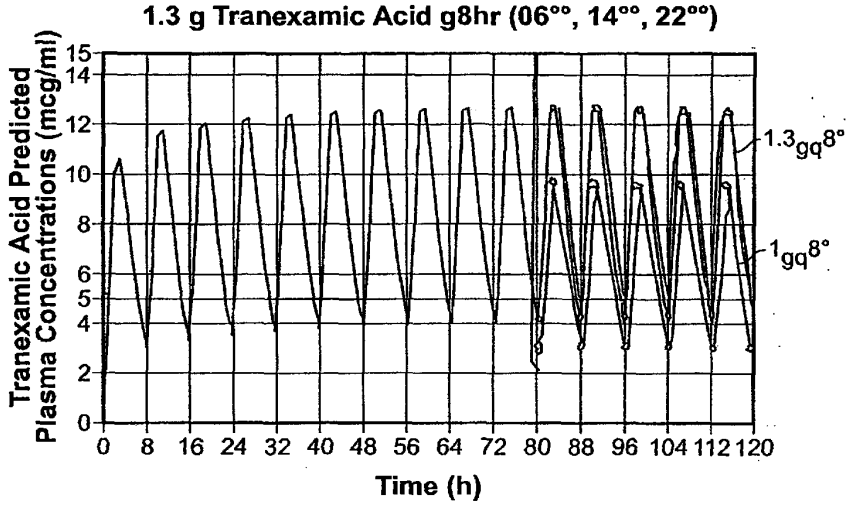
(57) **ABSTRACT**

Disclosed are modified release oral tranexamic acid formulations and methods of treatment therewith.

12 Claims, 3 Drawing Sheets



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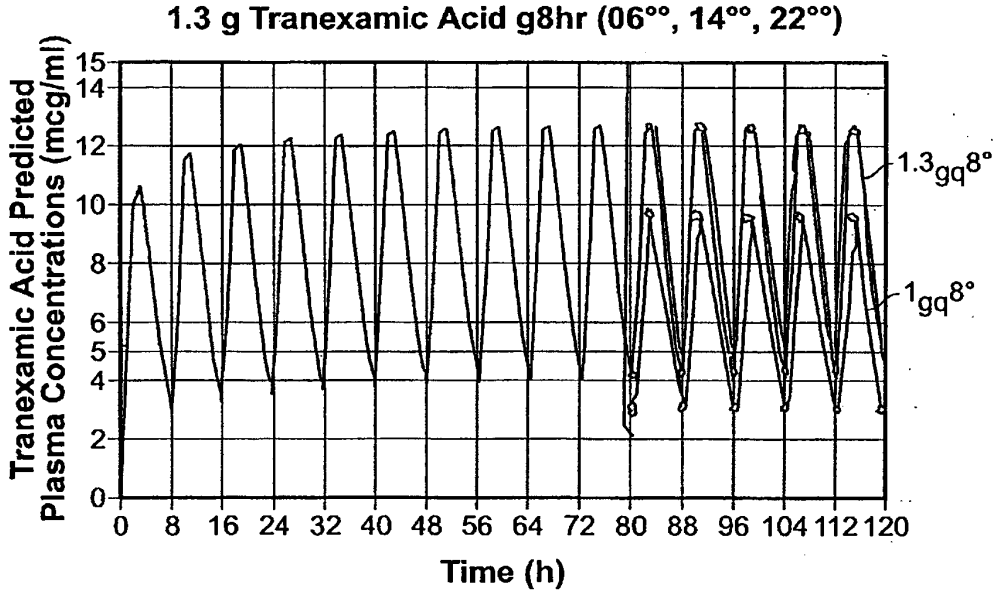

FIG. 1

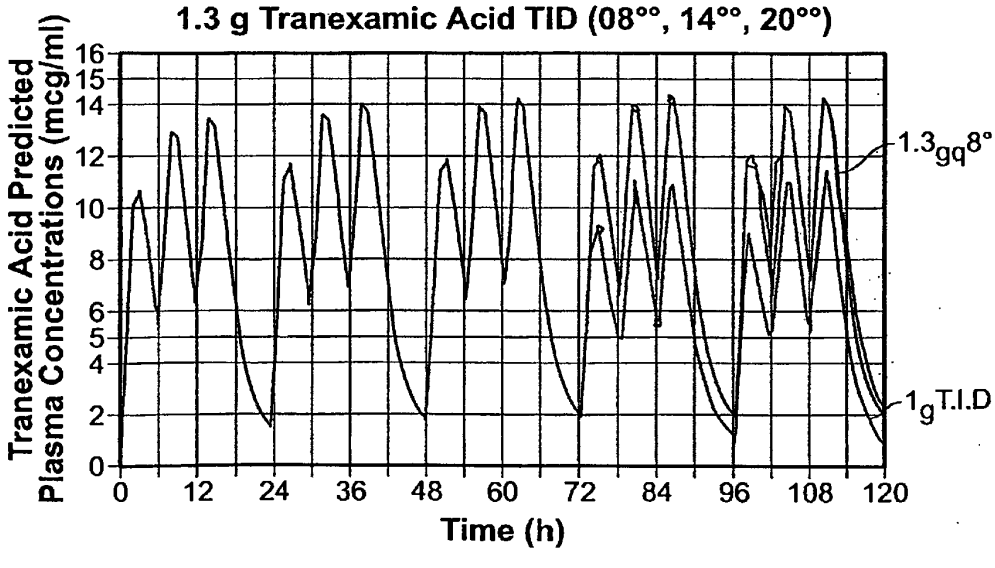

FIG. 2

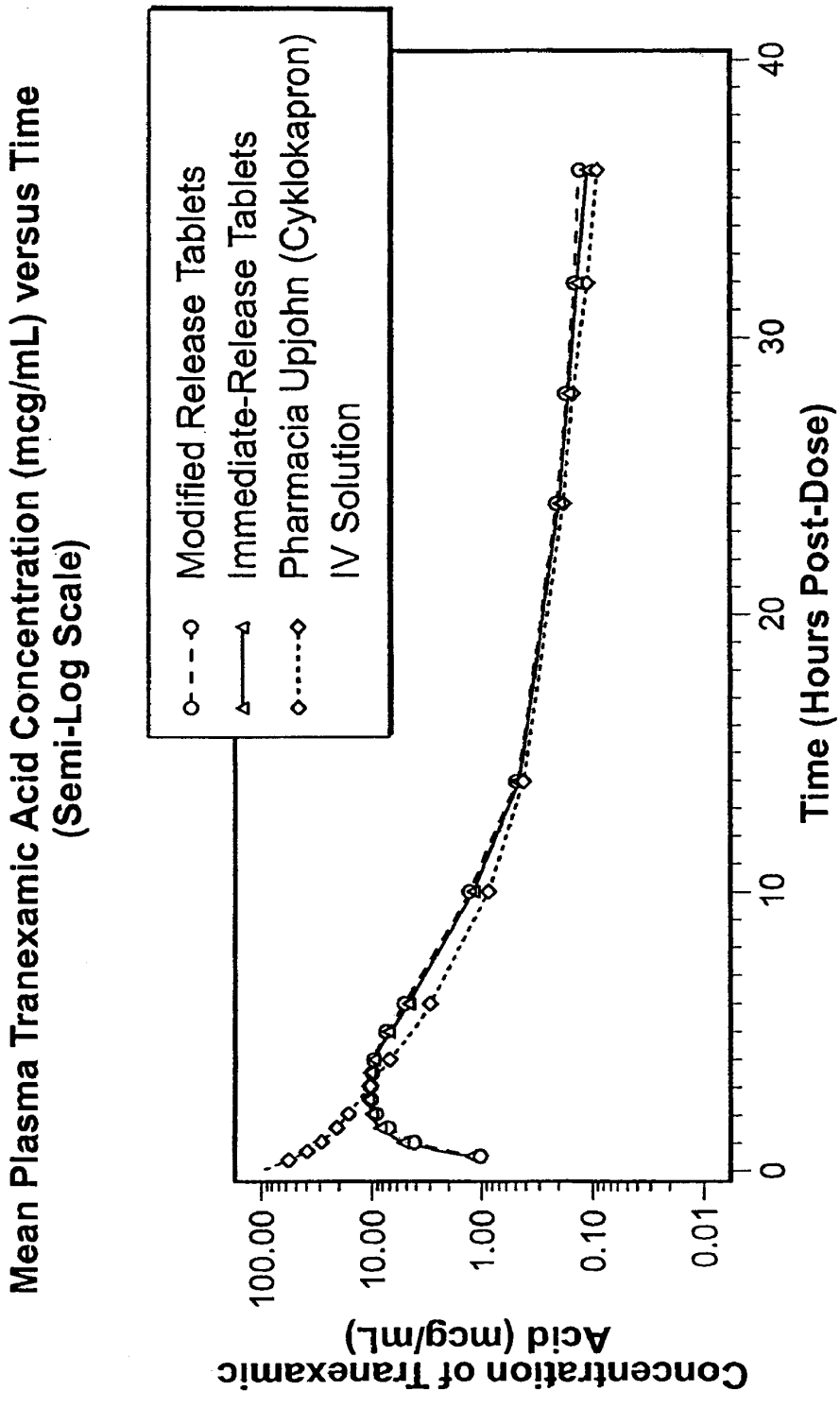

FIG. 3

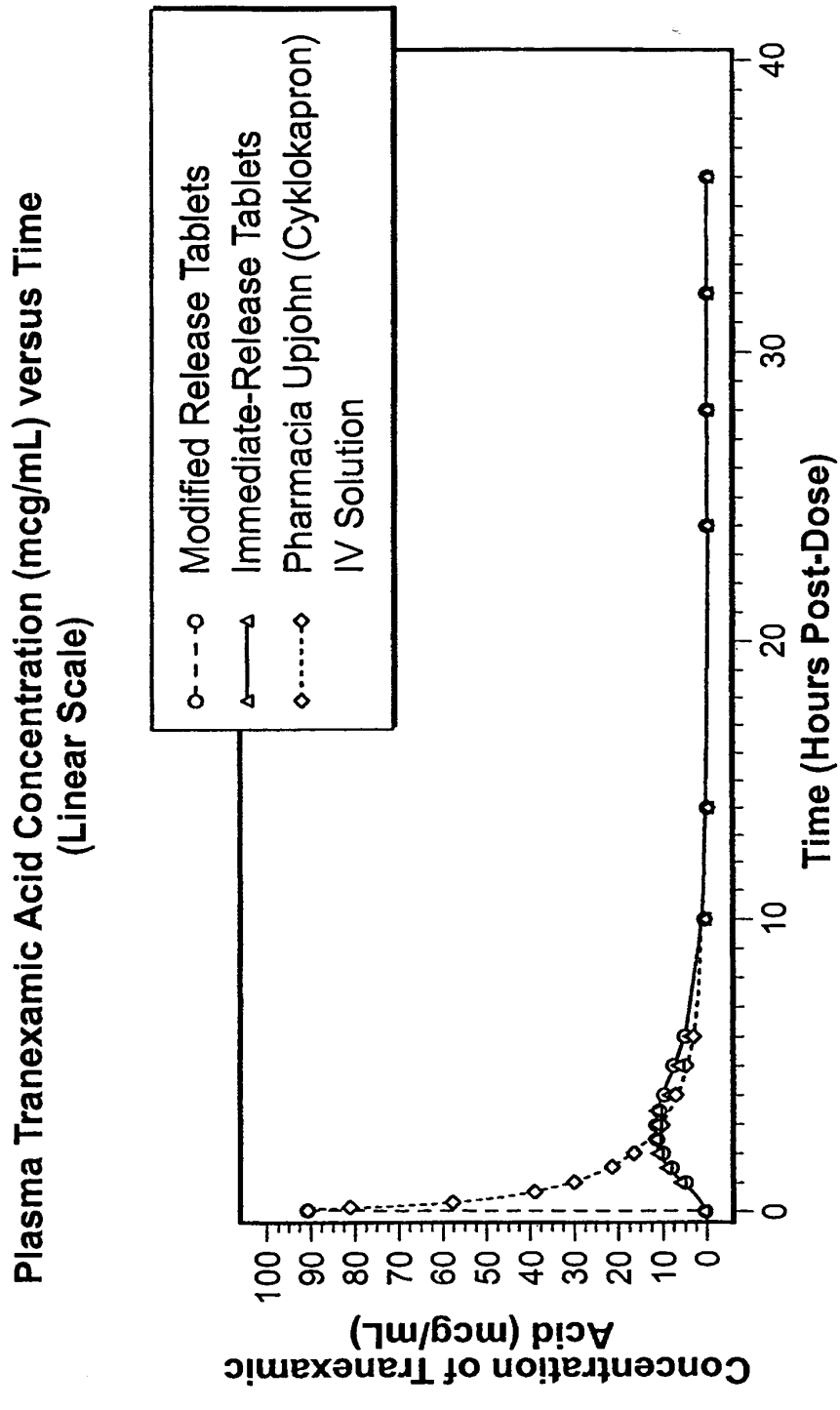

FIG. 4

TRANEXAMIC ACID FORMULATIONS

This application is a continuation of U.S. patent application Ser. No. 11/072,194 filed Mar. 4, 2005 which claims the benefit of U.S. Provisional Application No. 60/550,113, filed Mar. 4, 2004, and U.S. Provisional Application No. 60/592,885, filed Jul. 30, 2004, the disclosures of which are both hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

The invention is directed to modified release oral tranexamic acid formulations that preferably minimize or eliminate undesirable side effects and methods of treatment with these formulations.

BACKGROUND OF THE INVENTION

Tranexamic acid (trans-4-(aminomethyl)cyclohexanecarboxylic acid, Cyklokapron® (Pfizer) is an antifibrinolytic agent. That is, it helps to prevent lysis or dissolution of a fibrin clot which forms in the normal physiologic process of hemostasis. Its mechanism of action is as a competitive inhibitor of plasminogen activation, and as a noncompetitive inhibitor of plasmin; both plasminogen and plasmin are activators of fibrinolysis and active clot-lysing agents. Tranexamic acid thus helps to stabilize fibrin clots, which in turn maintains coagulation and helps to control bleeding.

Tranexamic acid is used to control excess bleeding, for example, excess bleeding that occurs during dental procedures in hemophiliacs and for heavy bleeding during menstruation (menorrhagia). Women suffering from menorrhagia are typically treated orally with 500 mg tranexamic acid tablets administered three or four times daily with a total daily dose ranging from 3 grams/day (two tablets every eight hours) to 6 grams/day (three tablets every six hours). However, this treatment may cause adverse gastrointestinal reactions, including nausea, vomiting, diarrhea, and cramping, etc. These gastrointestinal side effects are due to the quantity of tranexamic acid and/or rapid rate of release of tranexamic acid into the stomach with each dose, as well as the large quantity of excipients used in the tablet formulation that are introduced into the stomach. Such side effects, in addition to the cramping, bloating, pain, and other symptoms that may accompany menses, are undesirable, and a formulation of tranexamic acid is needed which will reduce or eliminate these side effects.

SUMMARY OF THE INVENTION

Formulations of tranexamic acid which minimize or eliminate the undesirable gastrointestinal side effects in patients on oral tranexamic acid therapy, e.g. women treated for menorrhagia (heavy menstrual bleeding) are disclosed. The present invention is directed in part to a modified release formulation, formulated so that the release of tranexamic acid thereof from the dosage form occurs in a designed fashion to prevent a bolus of tranexamic acid being introduced into the stomach and available for dissolution in the gastric contents. Such modified release formulations reduce the concentration of tranexamic acid dissolved in the stomach contents such as e.g., preventing a large bolus of tranexamic acid being introduced in the stomach. The beneficial effect of this reduced tranexamic acid concentration is to lower the amount of tranexamic acid in the gastric contents so that there are fewer adverse effects with tranexamic acid therapy. This reduction in adverse effects preferably results in improved patient compliance with therapy, because preferably patients will not intentionally miss taking a dose to avoid these adverse side effects. Physicians will also preferably be more likely to initiate and maintain tranexamic acid treatment for their patients because of the reduced patient complaints.

It is an object of the invention to provide an oral dosage form comprising tranexamic acid which is suitable for administration on a two or three times a day basis to humans.

It is a further object of the invention to provide a modified release oral dosage form comprising tranexamic acid and a modified release material which provides for the modified release of the tranexamic acid and is suitable for administration on a two or three times a day basis.

It is a further object of certain embodiments of the present invention to provide a modified release oral dosage form comprising tranexamic acid and a modified release material which minimizes or eliminates the undesirable gastrointestinal side effects in patients on oral tranexamic acid therapy while maintaining or improving the therapeutic effect of tranexamic acid.

It is a further object of certain embodiments of the present invention to provide a method of treating a patient suffering from heavy menstrual bleeding (menorrhagia) by orally administering to the patient one or more dosage forms comprising tranexamic acid and a modified release material which provide(s) for therapeutically effective levels of tranexamic acid suitable for two or three times a day administration.

The above advantages and objects and others can be achieved by virtue of the present invention which is directed in part to a modified release oral dosage form comprising tranexamic acid or a pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis; said dosage form providing an in-vitro dissolution release rate of the tranexamic acid or pharmaceutically acceptable salt thereof, when measured by a USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C., of less than about 70% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes and about 100% by weight of said tranexamic acid or pharmaceutically acceptable salt thereof released by about 120 minutes.

In certain embodiments, the present invention is directed to a method of treating a patient in need of tranexamic acid or pharmaceutically acceptable salt thereof therapy comprising administering to the patient about 1300 mg of tranexamic acid or pharmaceutically acceptable salt thereof in at least one oral dosage form comprising said tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides a mean maximum plasma concentration (C_{max}) of tranexamic acid of from about 5 to about 17.5 mcg/ml, preferably from about 6.5 to about 15 mcg/ml, more preferably from about 9 to about 14.5 mcg/ml after single dose oral administration to humans.

In certain embodiments, the invention is further directed to a method of treating a patient in need of tranexamic acid or pharmaceutically acceptable salt thereof therapy comprising administering to the patient about 1300 mg of tranexamic acid or pharmaceutically acceptable salt thereof in at least one oral dosage form comprising said tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides a mean maximum plasma concentration (C_{max}) of tranexamic acid of from about 5 to about 25 mcg/ml, preferably from about 10 to about 20 mcg/ml, more pref-

erably from about 12.5 to about 17.5 mcg/ml, most preferably about 15 to about 17 mcg/ml after steady state oral administration to humans.

In certain embodiments, the modified release oral dosage form of the present invention provides a mean T_{max} of tranexamic acid at from about 1 to about 5.5 hours, preferably at from about 2 to about 4 hours, more preferably at from about 2 to about 3.5 hours after oral administration of the dosage form to humans.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides a dissolution release rate invitro of the tranexamic acid or pharmaceutically acceptable salt thereof when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. of less than about 40% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, less than about 70% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, and not less than 50% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides a dissolution release rate invitro of the tranexamic acid or pharmaceutically acceptable salt thereof when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. of about 0% to about 40% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, from about 20% to about 60% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 30 minutes, from about 40% to about 65% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, from about 50% to about 90% by weight tranexamic acid or pharmaceutically acceptable salt thereof release at about 60 minutes, and not less than 60% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, which provides for a bioavailability of tranexamic acid of greater than 40%, from about 41% to about 60%, preferably from about 42% to about 50%, more preferably about 45% after oral administration to humans

In certain embodiments, the present invention is further directed to a modified release oral dosage form comprising from about 585 to about 715 mg of tranexamic acid or pharmaceutically acceptable salt thereof, preferably about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof, and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis.

In certain embodiments, the present invention is directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis, the dosage form providing a reduction of at least one side effect selected from the group consisting of headache, nausea, vomiting, diarrhea, constipation, cramping, bloating, and combinations thereof, as compared to an equivalent amount of tranexamic acid or pharmaceutically acceptable salt thereof in an immediate release oral dosage form when administered across a patient population.

In certain embodiments, the present invention is directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release excipient, said dosage form providing for the release of the tranexamic acid or pharmaceutically acceptable salt thereof which is slower than an immediate release oral dosage form and faster than a controlled release oral dosage form, such that the modified release oral dosage form is suitable for administration two or three times a day.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, the dosage form being suitable for oral administration on a three times a day basis, and the dosage form providing a mean maximum plasma concentration (C_{max}) of tranexamic acid of from about 5 to about 17.5 mcg/ml, preferably from about 6.5 to about 15 mcg/ml, more preferably from about 9 to about 14.5 mcg/ml per 1300 mg tranexamic acid after single dose oral administration to humans.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, the dosage form being suitable for oral administration on a twice a day basis, and the dosage form providing a mean maximum plasma concentration (C_{max}) of tranexamic acid of from about 5 to about 40 mcg/ml, preferably from about 10 to about 30 mcg/ml per 1950 mg tranexamic acid after single dose oral administration to humans.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, the dosage form being suitable for oral administration on a three times a day basis, and the dosage form providing a mean plasma concentration of tranexamic acid of from about 5 to about 25 mcg/ml, preferably from about 7.5 to about 15 mcg/ml, more preferably from about 8 to about 10 mcg/ml, most preferably about 9 mcg/ml per 1300 mg tranexamic acid after steady state oral administration to humans.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, the dosage form being suitable for administration on a three times a day basis, and the dosage form providing a mean maximum plasma concentration (C_{max}) of tranexamic acid of from about 5 to about 25 mcg/ml, preferably from about 10 to about 20 mcg/ml, more preferably from about 12.5 to about 17.5 mcg/ml, most preferably about 15 to about 17 mcg/ml per 1300 mg tranexamic acid after steady state oral administration to humans.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and an modified release material, the dosage form being suitable for administration on a three times a day basis, and the dosage form providing a mean plasma trough concentration of tranexamic acid or pharmaceutically acceptable salt thereof of from about 2 to about 10 mcg/ml, preferably from about 3 to about 7.5 mcg/ml, more preferably about 4 to about 7 mcg/ml, most preferably about 5 to about 6 mcg/ml per 1300 mg tranexamic acid or after steady state oral administration to humans.

In certain embodiments, the invention is further directed to a method of treating a patient with a therapeutically effective amount of tranexamic acid or pharmaceutically acceptable salt thereof comprising administering to the patient two dosage forms of the present invention, each dosage form comprising from about 585 mg to about 715 mg of tranexamic acid or pharmaceutically acceptable salt thereof, preferably about 650 mg tranexamic acid or pharmaceutically acceptable salt thereof, and a modified release material such that the dosage form is suitable for oral administration on a three times a day basis.

In certain embodiments, the invention is further directed to a method of treating a patient with a therapeutically effective amount of tranexamic acid or pharmaceutically acceptable salt thereof comprising administering to the patient three dosage forms of the present invention, each dosage form comprising from about 585 mg to about 715 mg, preferably about 650 mg tranexamic acid or pharmaceutically acceptable salt thereof, and a modified release material such that the dosage form is suitable for oral administration on a twice a day basis.

In certain embodiments, the invention is directed to a dose of tranexamic acid or pharmaceutically acceptable salt thereof comprising two unit dosage forms of a modified release formulation, each unit dosage form of said modified release formulation comprising from about 585 mg to about 715 mg, preferably about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof, and a modified release material which provides for the release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dose provides a therapeutic effect when administered three times a day.

In certain embodiments, the invention is directed to a dose of tranexamic acid comprising three unit dosage forms of a modified release formulation, each unit dosage form of said modified release formulation comprising from about 585 mg to about 715 mg, preferably about 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof, and a modified release material which provides for the release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dose provides a therapeutic effect when administered twice a day.

In certain preferred embodiments, the invention is further directed to a modified release oral dosage form including tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides a dissolution release rate in-vitro of the tranexamic acid or pharmaceutically acceptable salt thereof when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. of about 0% to about 40% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, from about 20% to about 60% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 30 minutes, from about 40% to about 80% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, from about 50% to about 95% by weight tranexamic acid or pharmaceutically acceptable salt thereof release at about 60 minutes, and not less than about 60% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes.

In certain preferred embodiments, the invention is further directed to a modified release oral dosage form including tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides a dissolution release rate in-vitro of the tranexamic acid or pharmaceutically acceptable salt thereof when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. of about 14% to about 22% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, from about 32% to about 50% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 30 minutes, from about 47% to about 71% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, from about 61% to about 92% by weight tranexamic acid or pharmaceutically acceptable salt thereof release at about 60 minutes, and from about 79% to about 100% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes.

In certain embodiments, the invention is directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and an effective amount of a modified release excipient such that the dosage form releases from about 10% to about 25% by weight tranexamic acid or pharmaceutically acceptable salt thereof every 15 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. In certain preferred embodiments, the dosage form releases about 18% to about 23% by weight tranexamic acid or pharmaceutically acceptable salt thereof every 15 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. Most preferably, the dosage form releases about 100% of said tranexamic acid or pharmaceutically acceptable salt thereof within about 120 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. In certain embodiments, the dosage form releases about 1% of said tranexamic acid or pharmaceutically acceptable salt thereof every minute when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C.

In certain preferred embodiments, the modified release oral dosage form of the invention further provides a mean transit time of said tranexamic acid of 7.70±0.72 hours when administered across a patient population.

In certain preferred embodiments, the modified release oral dosage form of the invention further provides a mean absorption time of said tranexamic acid of 4.18±0.70 hours when administered across a patient population.

In certain further embodiments, the modified release oral dosage form of the present invention provides confidence intervals derived from ln-transformed pharmacokinetic kinetic parameters AUC_{0-t}, AUC_{inf} and C_{max} for tranexamic

acid in plasma which are within a 80-125% range of an immediate release formulation including an equivalent amount of tranexamic acid when administered across a patient population under fasted conditions.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides less than about 20 percent incidence of headache as a side effect after single dose oral administration across a patient population.

In certain embodiments, the invention is further directed to a modified release oral dosage form comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which provides for the modified release of the tranexamic acid or pharmaceutically acceptable salt thereof from the dosage form such that the dosage form is suitable for administration on a two or three times a day basis and the dosage form provides less than about 10 percent incidence of nausea as a side effect when administered across a patient population, less than about 7 percent incidence of nausea when administered across a patient population, preferable less than about 5 percent incidence of nausea as a side effect when administered across a patient population, more preferably less than about 2 percent incidence of nausea as a side effect after single dose oral administration across a patient population.

In certain embodiments, the modified release oral dosage form of the present invention provides less CNS side effects (e.g., headache), less GI side effects (e.g., nausea), or combination thereof in comparison to an equivalent amount of tranexamic acid or pharmaceutically acceptable salt thereof in an immediate release formulation when administered across a patient population. Additionally or alternatively, in certain embodiments the dosage form provides less CNS side effects (e.g., headache), less GI side effects (e.g., nausea), or combination thereof in comparison to a therapeutically equivalent amount of tranexamic acid administered intravenously in five minutes or less across a patient population.

In certain embodiments, the modified release oral dosage form of the present invention provides for the reduction of at least one side effect as compared to an immediate release oral dosage form including an equivalent amount of tranexamic acid or pharmaceutically acceptable salt thereof, when the immediate release dosage form is administered across a same or different population of patients as said modified release dosage form, and wherein said immediate release dosage form releases all of said tranexamic acid or pharmaceutically acceptable salt thereof within about 45 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. Such side effects can be for example, headache, nausea, vomiting, diarrhea, constipation, cramping, bloating, and combinations thereof

In certain embodiments, the modified release oral dosage form of the present invention provides a mean transit time of tranexamic acid which is at least about 20 minutes longer, preferably about 30 minutes longer, than an immediate release formulation including an equivalent amount of tranexamic acid when administered across a patient population.

In certain embodiments, the dosage form of the present invention provides a mean absorption time of tranexamic acid which is at least about 20 minutes longer, preferably about 30 minutes longer, than an immediate release formulation including an equivalent amount of tranexamic acid when administered across a patient population.

In certain preferred embodiments, the therapeutically effective dose of the tranexamic acid or pharmaceutically acceptable salt thereof is provided via the administration of two or more dosage units. For example, if the dosage unit comprises 650 mg of tranexamic acid or pharmaceutically acceptable salt thereof and the dose for administration is about 1300 mg then two dosage units would be administered to a patient in need of such treatment, or for example, when the dose for administration is 1950 mg, three dosage units would be administered.

In certain preferred embodiments, the invention is further directed to a method of treating a patient with one or more modified release oral dosage forms comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, wherein the oral dosage form provides a therapeutically effective plasma level of tranexamic acid or pharmaceutically acceptable salt thereof in accordance with a three times a day (TID) dosing schedule, and the therapeutically effective dose administered comprises about 1300 mg of tranexamic acid or pharmaceutically acceptable salt thereof.

In certain preferred embodiments, the invention is further directed to a method of treating a patient with one or more modified release oral dosage forms comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material, wherein the oral dosage form provides a therapeutically effective plasma level of tranexamic acid or pharmaceutically acceptable salt thereof in accordance with a twice a day (BID) dosing schedule, and the therapeutically effective dose administered comprises about 1950 mg of tranexamic acid or pharmaceutically acceptable salt thereof.

In certain embodiments, the invention is directed to a method of providing a tranexamic acid plasma concentration within the range of about 5 mcg/mL to about 15 mcg/mL by administration of a modified release formulation of the present invention comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material on a three times a day basis to a patient in need of tranexamic acid or pharmaceutically acceptable salt thereof treatment.

In certain embodiments, the invention is further directed to a method of treating a human patient with heavy menstrual bleeding (e.g., menorrhagia) comprising administering about 1300 mg of tranexamic acid or pharmaceutically acceptable salt thereof on a three times a day basis to the human patient to provide a tranexamic acid or pharmaceutically acceptable salt thereof plasma concentration within the range of about 5 mcg/mL to about 15 mcg/mL after steady state oral administration to a human patient.

In certain embodiments, the invention is directed to a method of treating a patient suffering from menorrhagia, conization of the cervix, epistaxis, hyphema, hereditary angioneurotic edema, a patient with a blood coagulation disorder undergoing dental surgery, combinations thereof, and the like, by administering at least one dosage form of the present invention to the patient in need in tranexamic acid or pharmaceutically acceptable salt thereof therapy.

In certain embodiments, the invention is directed to a method of treating heavy menstrual bleeding with a therapeutically effective dose of at least one oral formulation of the present invention comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material wherein the menstrual blood loss per menstrual cycle is reduced by at least about 10 ml, preferably at least about 20 ml, more preferably at least about 40 ml. In a most preferred embodiment the menstrual blood loss per menstrual cycle is reduced by greater than or equal to about 50 ml.

In certain embodiments, the invention is directed to a method of treating heavy menstrual bleeding with a therapeutically effective dose of at least one oral formulation of the present invention comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which upon oral administration to a human female reduces the blood loss per menstrual cycle by about 35 ml to about 200 ml, preferably about 40 ml to about 175 ml, more preferably from about 50 ml to about 150 ml.

In certain embodiments, the invention is further directed to a method of treating heavy menstrual bleeding with a therapeutically effective dose of at least one oral formulation of the present invention comprising tranexamic acid or pharmaceutically acceptable salt thereof and a modified release material which upon oral administration to a human female reduces the blood loss per menstrual cycle by about 20% to 100%, preferably from about 20% to about 70%.

The menstrual blood loss can be measured by procedures known in the art. For example, in certain embodiments, the menstrual blood loss can be determined by a procedure described by (i) L. Hallbert, et al. in "Determination of Menstrual Blood Loss", *Scandinav. J. Clin. & Lab. Investigation,* 244-248, 16, 1964, wherein the procedure is performed by extracting the menstrual blood from vaginal tampons and towels with a sodium hydroxide solution, converting heme chromogens to alkaline hematin, which is determined spectrophotometrically; or (ii) the menstrual blood loss can be determined by a procedure described by J. Newton, M. D., et al., in "A Rapid Method for Measuring Menstrual Blood Loss Using Automatic Extraction.", *Contraception,* 269-282, September 1977, Vol. 16, No. 3, wherein the procedure is based upon the formation of alkaline haematin after the blood has been extracted from vaginal tampons and sanitary towels by an automatic Stomacher Lab-Blender. The disclosures of the aforementioned articles are hereby incorporated by reference in their entireties.

In certain embodiments, the modified release material may be incorporated in a coating applied onto e.g., a tablet comprising the tranexamic acid or pharmaceutically acceptable salt thereof, may be incorporated into a matrix with the tranexamic acid or pharmaceutically acceptable salt thereof, or a combination thereof. For example, in certain preferred embodiments, the modified release material is a controlled release material such as a gel-forming or hydratable polymer which is added to e.g., a matrix composition comprising the tranexamic acid or pharmaceutically acceptable salt thereof.

In certain embodiments, the tranexamic acid for use in the methods and formulations of the present invention is in the form of a pharmaceutically acceptable salt thereof. Such salt forms include for example and without limitation the sodium salt, potassium salt, calcium salt, magnesium salt and the like; as well as the hydrochloride, hydrobromide, sulfate, phosphate, formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate-methanesulfonate salt forms, and the like. Preferably the active ingredient for use in accordance with the present invention is tranexamic acid.

An "immediate release oral dosage form" for purposes of the present invention is a dosage form which releases all of active ingredient (e.g., tranexamic acid) included therein within about 45 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C.

A "modified release oral dosage form" for purposes of the present invention is an oral dosage form which releases the active ingredient (e.g., tranexamic acid) included therein in a manner that is slower than an immediate release oral dosage form and faster than a controlled release oral dosage form, when the dosage forms include the same amount of active as the modified release oral dosage form. One definition of the terms "slower" and "faster" as used in this application is that they are meant to represent a statistically significant difference at each measured 15 minute interval after the start of in-vitro dissolution. In certain preferred embodiments, the modified release oral dosage form of the present invention provides an in-vitro dissolution release rate of tranexamic acid or pharmaceutically acceptable salt thereof, when measured by a USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C., of less than about 70% by weight tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes and about 100% by weight of said tranexamic acid or pharmaceutically acceptable salt thereof released by about 120 minutes.

A "controlled release oral dosage form" for purposes of the present invention is a dosage form which releases all of the active ingredient (e.g., tranexamic acid) included therein after about 4 hours or more when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C.

The term "C_{max}" unless otherwise indicated is meant for purposes of the present invention to mean the maximum plasma concentration of a medicament achieved after single dose administration of a dosage form, or the maximum plasma concentration of a medicament achieved over a dosing interval from multiple-doses at steady-state in accordance with the present invention.

The term "T_{max}" is meant for purposes of the present invention to mean the elapsed time from administration of a dosage form to the time the C_{max} of the medicament is achieved.

The term "steady state" means that the amount of the drug reaching the system is approximately the same as the amount of the drug leaving the system. Thus, at "steady-state", the patient's body eliminates the drug at approximately the same rate that the drug becomes available to the patient's system through absorption into the blood stream.

The term "mean" for purposes of the present invention, when used to define a pharmacokinetic value (e.g., T_{max}), unless specified otherwise, represents the arithmetic mean value measured across a patient or subject population.

The term "three times a day (TID) basis" for purposes of the present invention, means that the dosage regimen is to be administered three times a day, preferably on a schedule of every 8 hours.

The term "mean transit time" is understood by those skilled in the art and means the time-point where 63.2% of the total AUC is attained after oral administration, or 63.2% of the IV dose is eliminated, as described in *Applied Pharmacokinetics, Principles of Therapeutic Drug Monitoring*, Second Edition (1986), edited by William E. Evans, et al., the disclosure of which is hereby incorporated by reference in its entirety.

The term "mean absorption time" is understood by those skilled in the art and means a quantitative parameter which summarizes how long, on average, the drug molecule remains unabsorbed, i.e. persists in its dosage form and in the gastrointestinal tract, also as described in *Applied Pharmacokinetics. Principles of Therapeutic Drug Monitoring*, Second Edition (1986), edited by William E. Evans, et al. Unlike the absorption rate constants (ka) which can be skewed, the mean absorption time is not affected by incomplete release of drug from its dosage form, irregular absorption, lag-time, mixed zero-order dissolution rates, changing GI motility, GI blood flow, first-pass effect, etc.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** depicts concentration-time profiles for simulated administration of the 1.3 g tranexamic acid modified release

formulation of Example 1 at a Q8H (every 8 hours) dosing schedule of 6:00 AM, 2:00 PM, 10:00 PM comparing it with 1 g administered Q8 H.

FIG. **2** depicts concentration-time profiles for simulated administration of the 1.3 g tranexamic acid modified release formulation of Example 1 at a TID (three times a day) dosing schedule of 8:00 AM, 2:00 PM, 8:00 PM comparing it with 1 g administered TID.

FIG. **3** depicts mean plasma concentration-time profiles on a semi-log scale over 36 hours for the study of Example 4.

FIG. **4** depicts mean plasma concentration-time profiles on a linear scale over 36 hours for the study of Example 4.

DETAILED DESCRIPTION

The dosage regimen typically listed for tranexamic acid in HMB (Heavy Menstrual Bleeding) therapy is 1-1.5 g per dose administered three-four times a day at the onset of copious menstrual bleeding and continued for the first 3-5 days of the menstrual cycle. However, the most frequently reported dosage regimen of tranexamic acid is an immediate release oral formulation in which 1 g tranexamic acid is administered four times a day (4 g per day) for HMB therapy outside of the US. Knowledge of this common regimen is supported by a careful review of the randomized controlled trials published in the medical literature, product labeling from other countries' regulatory authorities having the product approved for HMB therapy, utilization data from Sweden (Rybo 1991), correspondence and interviews with non-US clinicians having experience with the product. That regimen is currently the dosage being studied by the US Center for Disease Control (CDC) in women with HMB associated with bleeding disorders.

The absolute bioavailability of tranexamic acid observed when administering the European commercial formulation (Cyklokapron, Kabi AB, Sweden Batch 90288; assay 499 mgm/tablet) to male subjects is approximately 35% and its elimination correlates with renal creatinine clearance. Peak serum tranexamic acid concentrations occur approximately 3 hours after the oral administration of a European immediate-release tablet formulation (>85% dissolved at 15 minutes) (Pilbrant, et al., *Eur. J. Clin. Pharmacol*, (1981)-20:65-72). By comparison, the in vivo absorption profile observed with the European immediate-release formulation is slow and very gradual over 3 hours. Specifically, tranexamic acid serum concentrations are 9, 41, 73, 88 percent (with food), and 22, 63, 85, and 98 percent (fasting) of maximal absorption at 0.5, 1, 1.5 and 2 hours after a 2 g oral dose, respectively. Although not wishing to be held to any specific theory, it is presently hypothesized that tranexamic acid oral absorption appears to be controlled by a non-dissolution rate limited process, i.e. the rate and extent of oral absorption is a function of a transmembrane passage-limited process, in order to explain the disparity between the time of product dissolution and relatively prolonged tmax (time to achieve the peak serum concentration).

Preferably, the goal of the formulation, dose strength and dosage regimen of the invention, is to provide HMB therapy which achieves from about 20% to 100% reduction in menstrual blood loss per menstrual cycle. In accordance with certain embodiments of the present invention, the preferred tranexamic acid dose of 1.3 g every 8 hours is predicted to provide an average serum tranexamic acid concentration comparable to that produced by a 1 g every 6 hour regimen (i.e. 12.4 mcg/mL), with associated peaks and troughs falling approximately within the therapeutic antifibrinolytic range (5-15 mcg/mL; Cyklokapron NDA 19-280). In certain embodiments, a two-compartment oral absorption and elimination simulation model coupled with pharmacokinetic data (Pilbrant, et al., *Eur. J. Clin. Pharmacol*, (1981)-20:65-72), and modified-release tablet dissolution performance information were used to determine the preferred lead dosage regimen.

In immediate release formulations the entire dose and the soluble components in the dosage form dissolve in gastrointestinal fluid and present a high concentration of solutes for absorption. The most frequently reported adverse effects are primarily confined to the proximal gastrointestinal tract (nausea and vomiting). These adverse symptoms appear to be related to the drug load presented to the gastric mucosa, since this effect can be minimized by reducing the immediate-release oral formulation dose or administering the product slowly by the intravenous route. In certain embodiments, a lower incidence of proximal gastrointestinal adverse effects is obtained with the preferred oral modified release formulation (e.g., dosed 1.3 g every 8 hours) of the invention, e.g., because of the modified release properties of the drug product formulation.

In certain embodiments, the oral dosage form of the present invention provides for an increased bioavailability as compared to immediate release oral dosage forms currently available (e.g., Cyclokapron). In certain preferred embodiments the increased bioavailability allows therapeutic plasma levels of tranexamic acid to be reached with a lower dose of drug. Preferably, the increased bioavailability also decreases the amount of tranexamic acid that remains unabsorbed in the gastrointestinal which leads to decreased incidence of side effects that are typically associated with formulations that provide higher levels of unabsorbed tranexamic acid and prolonged exposure of the gastrointestinal tract to the higher tranexamic acid levels. Preferably the oral dosage form of the present invention provides for a bioavailability of tranexamic acid of greater than 40%, from about 41% to about 60%, preferably from about 42% to about 50%, more preferably about 45% after oral administration to humans.

The modified release oral formulations of tranexamic acid of the present invention provides a release of the drug which is slower than that of the immediate release 500 mg Cyklokapron product current marketed in Canada which provided a mean release rate of 100% by weight tranexamic acid released by about 15 minutes when measured utilizing USP 27 Apparatus Type II paddle method @ 50 RPM in 900 ml water at 37±0.5° C.

In certain embodiments, the modified release oral formulations may be described as providing a mean transit time through the proximal gastrointestinal mucosa which takes approximately one half hour longer than an immediate release formulation. In other preferred embodiments, the modified release formulations of the invention provide a rate of release of (dissolved) tranexamic acid from the dosage form in-vitro which is approximately 20, 40, 60, 80, and 100 percent of the total dose at 0.25, 0.5, 0.75, 1 and 1.5 hours, respectively. In certain preferred embodiments, such a release rate in-vitro demonstrates that the formulations of the present invention provide a relative reduction in the amount and rate of dissolved tranexamic acid presented to the proximal gastric mucosa to approximate 20, 40, 60, 80, and 100 percent of the total dose at 0.25, 0.5, 0.75, 1 and 1.5 hours, respectively, after oral administration.

In certain embodiments, the majority of tranexamic acid absorption appears to occur slowly distal to the stomach, and assuming linear pharmacokinetics, the modified release formulation produces an absorption profile which is comparable

to that achieved with the currently available oral immediate release formulations used outside the U.S.

In accordance with the present invention a modified release tranexamic acid tablet for oral administration is disclosed. Preferably, the tablet contains at least one material (defined herein as any substance other than the active, i.e., tranexamic acid) which minimizes or eliminates the adverse gastrointestinal side effects in patients, for example, women dosed with oral tranexamic acid for treatment of menorrhagia.

The modified release oral dosage forms of tranexamic acid for purposes of the present invention include formulation ingredients and/or configurations which are typically utilized for formulations known in the art as extended, sustained and controlled release formulations, although modified to provide a desirable release rate in keeping with the teachings of the present invention. The modified release formulations preferably decrease the concentration of tranexamic acid and materials dissolved in the stomach fluids after dosing by controllably releasing tranexamic acid over a period of time, as opposed to immediate release formulations which release the entire dose of tranexamic acid all at once. The modified release formulations of the present invention thus minimize or prevent gastrointestinal reactions and side effects that occur when a dose of tranexamic acid is ingested and immediately reaches the stomach.

The modified release dosage forms of the present invention may be prepared as; tablets, capsules, granules, pellets, powders, dragees, troches, non-pariels, pills or encapsulated suspension, and may be packaged into capsules, sachets, etc. Such dosage forms may be prepared by any formulation technique where release of the active substance (tranexamic acid) from the dosage form is modified to occur at a slower rate than from an immediate release product. In these formulations, tranexamic acid release occurs in the stomach and/or intestine, but at a slower rate so that a bolus of dissolved drug does not reach the lining of the stomach and cause adverse effects, or adverse effects occur with a lower intensity or frequency because of the lower concentration of tranexamic acid. Hence, adverse effects are preferably reduced, minimized or eliminated.

Methods of preparing modified release formulations are found in Modified Release Drug Delivery Technology, Rathbone, Hadgraft, and Roberts, Eds., Drugs and the Pharmaceutical Sciences, Vol. 126, Marcel Dekker Inc., New York, 2003; Modern Pharmaceutics, Third Edition, Banker and Rhodes, Eds. Drugs and the Pharmaceutical Sciences, Vol. 72, Marcel Dekker Inc., New York, 1996; Sustained and Controlled Release Drug Delivery Systems, Robinson, Ed., Drugs and the Pharmaceutical Sciences, Vol. 6, Marcel Dekker Inc., NY 1978; Sustained Release Medications, Chemical Technology Review No. 177, Johnson, Ed., Noyes Data Corporation 1980; Controlled Drug Delivery, Fundamentals and Applications, Second Edition, Robinson and Lee, Eds., Marcel Dekker Inc., New York, 1987, and as described in U.S. Pat. No. 6,548,084, each of these references being expressly incorporated by reference herein in its entirety.

Preferably, a modified release form, makes tranexamic acid available over an extended period of time after ingestion. Modified release dosage forms coupled with the digestion process and the absorption process in the gastrointestinal tract cause a reduction in the amount of tranexamic acid in solution in the gastrointestinal tract compared to dosing tranexamic acid presented as a conventional dosage form (e.g., as a solution, or as an immediate release dosage form). The modified release formulation may be verified by in vitro dissolution testing and in vivo bioequivalence documentation, according to Food and Drug Administration standards, e.g., as set forth at www.fda.gov, 21 CFR §314, 320, and also at USP 23 NF 18 §711, 724. For example, an in vitro dissolution test such as USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. may be used to verify the release of the tranexamic acid from the dosage form.

Tranexamic acid modified release tablets may be formulated to provide a dose of tranexamic acid, typically about 500 mg to about 2 grams from one to two tablets, within about the first one to two hours after the tablet is ingested. Thus, tranexamic acid release occurs at a designed rate over a period e.g., about 60 minutes to about 120 minutes. The rate of tranexamic acid release over this period of time is designed to provide a reduced concentration of tranexamic acid in the stomach while allowing the absorption of tranexamic acid to occur throughout the gastrointestinal tract. Absorption of tranexamic acid typically begins as soon as tranexamic acid is released from the dosage form and is dissolved in the gastrointestinal fluids contacting the membranes which line the gastrointestinal tract. The rate of release of tranexamic acid from the dosage form and the absorption of drug by the gastrointestinal mucosa help to maintain low concentrations of drug in the gastrointestinal fluids. The lowered concentrations preferably result in lower intensity, frequency, and/or severity of gastrointestinal adverse side effects. The designed rate of release of tranexamic acid from the dosage form in the stomach and the upper small intestine, the natural emptying of gastric juice containing any dissolved tranexamic acid from the stomach, and the absorption of tranexamic acid from a larger segment of the gastrointestinal tract (i.e., both the stomach and the small intestine, rather than the stomach only or the lower portion of the small intestine if any modified release dosage form with a longer release time was used), preferably results in reduced levels of dissolved tranexamic acid in the region of the gastrointestinal tract proximal or distal to the dosage form. Reduced concentrations of tranexamic acid along the gastrointestinal tract preferably provide a reduction in adverse gastrointestinal effects associated with oral tranexamic acid therapy.

As used herein, alleviation of adverse effects using these formulations indicates any relief in one or more symptoms, such as decrease in incidence, severity, or duration of symptoms, and is not limited to absence of symptoms or elimination of symptoms. Thus, treatment includes any decrease in incidence, duration, intensity, frequency, etc. of adverse gastrointestinal symptoms including, but not limited to, headache, nausea, vomiting, diarrhea, constipation, cramping, bloating, and combinations thereof. The formulations may reduce symptoms at any time during tranexamic acid therapy, but minimized adverse effects are particularly noted immediately or shortly after dosing, that is, within the first few hours after dosing. As used herein, adverse gastrointestinal effects and side effects are used interchangeably to indicate nontherapeutic effects (i.e., not relating to any possible beneficial effects due to tranexamic acid), ranging from unpleasant but tolerable sensations to severe gastrointestinal symptoms. As used herein, the terms oral formulations, ingestible formulations, and orally administered formulations are used interchangeably and include any dosage forms which are ingested by mouth, including, but not limited to, tablets, pills, liquids, gelcaps, softgels, dragees, capsules, powders, granules, pellets, etc.

Modified release formulations of tranexamic acid include tablets, pellets, granules, capsules, or other oral dosage forms prepared in such a way to release tranexamic acid in a designed manner. In certain embodiments, the modified

release material is a gel-forming polymer, a hydratable polymer, a water soluble polymer, a water swellable polymer, or mixtures thereof.

In certain embodiments, modified release tranexamic acid tablets are prepared by adding a modified release material comprising a gel-forming or hydratable polymer to a tranexamic tablet composition. Suitable gel-forming or hydratable polymers include, but are not limited to, hydroxypropylcellulose, hydroxypropylmethylcellulose or hypromellose, carboxymethylcellulose, polyvinyl alcohol, etc. This provides a compressed tablet that may or may not be film coated. The tablet releases tranexamic acid by diffusion of tranexamic acid through the tablet matrix, or by erosion of the tablet matrix, or by a combination of diffusion from and erosion of the tablet matrix. Tablets formed with water swellable polymers release tranexamic acid by diffusion of tranexamic acid through the tablet matrix, or by erosion of the tablet matrix, or by a combination of diffusion from and erosion of the tablet matrix. One or more water-soluble hydrophilic polymer(s) may also be used. These include polyvinylpyrrolidine, hydroxypropyl cellulose, hydroxypropylmethylcellulose, now referred to as hypromellose (e.g., Methocel™, Dow Chemical Company), methyl cellulose, vinyl acetate/crotonic acid copolymers, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers, derivatives thereof and mixtures thereof. In various embodiments, the polymer is hydroxypropyl cellulose or hydroxypropylmethylcellulose. The polymer may be hydroxypropyl-methyl cellulose with a viscosity ranging from about 50 cps to about 200 cps. The polymer may be hydroxypropyl-methyl cellulose with a viscosity of 100 cps, commercially available as Methocel™ K 100 LV (Dow Chemical Company). The amount of polymer in the composition may be in the range of about 5% by weight to about 50% by weight of the composition. In various embodiments, the polymer is in the range of about 10% by weight to about 35% by weight of the composition, or about 10% by weight to about 30% by weight of the composition.

In certain embodiments the modified release material comprises a vinyl polymer, phthalic acid derivative of vinyl copolymer, hydroxyalkylcellulose, alkylcellulose (e.g., ethylcellulose), cellulose acetate, hydroxyalkylcellulose acetate, cellulose ether, alkylcellulose acetate and partial esters thereof, and polymers and copolymers of lower alkyl acrylic acids and lower alkyl acrylates and partial esters thereof, or combination thereof. In preferred embodiments the modified release material comprises hydroxypropylcellulose, hydryoxpropylmethylcellulose, carboxymethylcellulose, polyvinyl alcohol, polyvinylpyrrolidone, methylcellulose, vinyl acetate/crotonic acid copolymers, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers, derivatives thereof, and mixtures thereof. In further preferred embodiments the modified release material comprises a polymer such as a methacrylic acid copolymer. These are copolymers of methacrylic acid with neutral acrylate or methacrylate esters such as ethyl acrylate or methyl methacrylate.

In certain embodiments the modified release material comprises a pH independent binder or film-forming agent such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, polyvinylpyrrolidone, neutral poly(meth) acrylate esters (e.g., the methyl methacrylate/ethyl acrylate copolymers sold as Eudragit® (Rohm Pharma), starches, gelatin, sugars such as glucose, sucrose, and mannitol, silicic acid, carboxymethylcellulose, and the like, diluents such as lactose, mannitol, dry starch, microcrystalline cellulose and the like, surface active agents such as polyoxyethylene sorbitan esters, sorbitan ethers, and the like, coloring agents, flavoring agents, lubricants such as talc, calcium stearate, and magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and other tableting aids. Any combination of the aforementioned binders or film-forming agents may be included in the modified release material. The modified release material may be combined with tranexamic acid to form modified release dosage forms.

In certain embodiments, the formulation includes tranexamic acid in the range of about 50% by weight to about 95% or more by weight of the formulation. In other embodiments, tranexamic acid is in the range of about 60% by weight to about 90% by weight, or about 60% by weight to about 80% by weight of the formulation. The remaining weight may be made up of the modified release material and additional excipients.

To prepare modified release tablet formulations, the agent or modified release material to slow the release of tranexamic acid may be incorporated into the tablet matrix or coated onto the tablet surface or both. In certain embodiments, tablet formulations prepared are formulated by granulating a blend of powders of the modified release material. The powder blend is formed by combining portions of the powdered components that make up the tablet. These powders are intimately mixed by dry-blending. The dry blended mixture is granulated by wet mixing of a solution of a binding agent with the powder blend. The time for such wet mixing may be controlled to influence the dissolution rate of the formulation. For example, the total powder mix time, that is, the time during which the powder is granulated, may range from about 1 min to about 10 min, or from about 2 min to about 5 min. Following granulation, the particles are removed from the granulator and placed in a fluid bed dryer, a vacuum dryer, a microwave dryer, or a tray dryer for drying. Drying conditions are sufficient to remove unwanted granulating solvent, typically water, or to reduce the amount of granulating solvent to an acceptable level. Drying conditions in a fluid bed dryer or tray dryer are typically about 50 to 70° C. The granulate is dried, screened, mixed with additional excipients such as disintegrating agents, flow agents, or compression aids and lubricants such as talc, stearic acid, or magnesium stearate, and compressed into tablets.

In certain embodiments, the tablet that contains a modified release material within the tablet matrix may be coated with an optional film-forming agent. This applied film may aid in identification, mask an unpleasant taste, allow desired colors and surface appearance, provide enhanced elegance, aid in swallowing, aid in enteric coating, etc. The amount of film-forming agent may be in the range of about 2% tablet weight to about 4% tablet weight. Suitable film-forming agents are known to one skilled in the art and include hydroxypropyl cellulose, cellulose ester, cellulose ether, one or more acrylic polymer(s), hydroxypropyl methylcellulose, cationic methacrylate copolymers (diethylaminoethyl)methacrylate/methyl-butyl-methacrylate copolymers such as Eudragit E® (Rohm Pharma) and the like. The film-forming agents may optionally contain colorants, plasticizers, fillers, etc. including, but not limited to, propylene glycol, sorbitan monooleate, sorbic acid, titanium dioxide, and one or more pharmaceutically acceptable dye(s).

In certain embodiments, the tranexamic acid tablets of the invention are coated with a modified release material. In certain embodiments, tranexamic acid tablets are formulated by dry blending, rotary compacting, or wet granulating powders composed of tranexamic acid and tablet excipients. These powders are compressed into an immediate release tablet. Coating this immediate release tablet with a modified release material as described herein renders this tranexamic acid tablet as a modified release tablet.

In addition to the modified release material, the formulations of the invention may also contain suitable quantities of other materials, e.g. preservatives, diluents (e.g., microcrystalline cellulose), lubricants (e.g., stearic acid, magnesium stearate, and the like), binders (e.g., povidone, starch, and the like), disintegrants (e.g., croscarmellose sodium, corn starch, and the like), glidants (e.g., talc, colloidal silicon dioxide, and the like), granulating aids, colorants, and flavorants that are conventional in the pharmaceutical art. Specific examples of pharmaceutically acceptable excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (2003), incorporated by reference herein.

The release process may be adjusted by varying the type, amount, and the ratio of the ingredients to produce the desired dissolution profile, as known to one skilled in the art. A coating may be a partially neutralized pH-dependent binder that controls the rate of tranexamic acid dissolution in aqueous media across the range of pH in the stomach, which has a pH of about 2, and the intestine, which has a pH of about 5.5 in its upper region. In certain embodiments, one or more pH dependent binders may be used to modify the dissolution profile so that tranexamic acid is released slowly and continuously as the formulation passes through the stomach and/or intestines.

In one embodiment, compressed modified release tablets are formulated to comply with USP criteria and to be of such a size and shape to be easy to swallow. The size of the tablet will depend upon the dose of tranexamic acid that is needed to provide adequate therapy and the particular formulation and excipients that are selected to provide the physical properties necessary for tableting and for modified release. In various embodiments, a compressed modified release tablet contains from about 500 mg to about 1 gram of tranexamic acid, or from about 600 mg to about 750 mg of tranexamic acid. The daily dose of tranexamic acid may be achieved by taking one or two tablets at each dosing time.

In certain embodiments, the tranexamic acid included in the dosage form is from about 375 mg to about 1500 mg, preferably from about 375 mg to about 1000 mg. In one embodiment, the dose of tranexamic acid per tablet is in the range of about 500 mg to about 1000 mg for tablets and from about 500 mg to about 1500 mg for a sachet filled with granules. In another embodiment, the dose of tranexamic acid is in the range of about 3 grams/day to about 6 grams/day in three or four divided doses. As an example, a total daily dose of 3 grams tranexamic acid may be divided into three doses of one tablet each with each tablet containing 1 gram tranexamic acid, or may be divided into four doses of one tablet each with each tablet containing 0.75 gram tranexamic acid. As another example, a total daily dose of 4 gram tranexamic acid may be divided into three doses of two tablets at each dose with each tablet containing 0.666 gram tranexamic acid, or may be divided into four doses of one tablet each with each tablet containing 1 gram tranexamic acid. As another example, a total daily dose of 5 gram tranexamic acid may be divided into three doses of one tablet each with each tablet containing 1.66 gram tranexamic acid, or may be divided into four doses of two tablets each with each tablet containing 0.625 gram tranexamic acid. As another example, a total daily dose of 6 gram tranexamic acid may be divided into three doses of two tablets each with each tablet containing 1 gram tranexamic acid, or may be divided into four doses of two tablets each with each tablet containing 0.75 gram tranexamic acid. For ease of swallowing, the dose of tranexamic acid taken at each dosing time may be delivered by taking multiple tablets. For example, the 4 gram daily dose may be delivered by taking two 666.67 mg tablets three times a day or two 500 mg tablets four times a day. Similarly, the 3 gram daily dose may be achieved by taking two 550 mg tablets three times a day or two 375 mg tablets four times a day. Alternatively, for ease of reference, a dose of 600 mg, 650 mg, or 700 mg of tranexamic acid per tablet may be used. In a preferred embodiment, a total daily dose of 3900 mg/day is administered in three divided doses of 1300 mg of two tablets at each dose with each tablet containing 650 mg of tranexamic acid. Alternatively, each dose may be delivered by taking granules containing the prescribed amount of tranexamic acid presented in a convenient unit dose package. Such examples are not limiting and other doses within these ranges will be appreciated by those skilled in the art.

Alternatively, modified release tranexamic acid formulations may be administered by pellets or granules in e.g., a sachet or capsule. Modified release tranexamic acid pellets or granules may be prepared by using materials to modify the release of tranexamic acid from the granule or pellet matrix. Modified release preparations may also be formulated using coatings to modify the release of tranexamic acid from the granule or pellet. U.S. Pat. Nos. 5,650,174; and 5,229,135 each of which is expressly incorporated by reference herein in its entirety, disclose variations on fabricating a pellet or non-pareil dosage form. Spheres are filled into packets, termed sachets, or capsules which are filled by weight to contain the prescribed dose of drug. Multiparticulates may be coated with an modified release coating, as disclosed in U.S. Pat. No. 6,066,339, which is expressly incorporated by reference herein its entirety. Coated multiparticulates may be packaged in capsules or sachets. The formulation of granules or pellets for modified release is described in Multiparticulate Oral Drug Delivery, Ghebre-Sellassie, Ed. in Drugs and the Pharmaceutical Sciences, Vol. 65 Marcel Dekker Inc. NY, 1994 and in the relevant parts of the references for modified release formulations previously cited and the relevant portions incorporated herein by reference.

In certain embodiments, the inventive tranexamic acid formulations may be used for additional indications other than menorrhagia, such as conization of the cervix, epistaxis, hyphema, hereditary angioneurotic edema, a patient with a blood coagulation disorder undergoing dental surgery, combinations thereof, and the like.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention will be further appreciated with respect to the following non-limiting examples. Other variations or embodiments of the invention will also be apparent to one of ordinary skill in the art from the above descriptions and examples. Thus, the forgoing embodiments are not to be construed as limiting the scope of this invention.

Example 1

Modified release 650 mg tranexamic acid tablets were prepared having the ingredients listed in the Table 1 below:

TABLE 1

Ingredient	Quantity per batch (kg)	Quantity per tablet (mg)
Active Ingredient		
Tranexamic Acid, EP	84.50	650.0
Inactive Ingredients		
Microcrystalline Cellulose NF (Avicel PH 101)	5.753	44.25
Colloidal Silicon Dioxide NF	0.0975	0.75
Pregelatinized Corn Starch, NF	6.435	49.50
Hypromellose, USP (Methocel K3 Premium LV)	19.110	147.00

TABLE 1-continued

Ingredient	Quantity per batch (kg)	Quantity per tablet (mg)
Povidone, USP (K value range 29-32)	4.680	36.00
Stearic Acid, NF (powder)	2.340	18.00
Magnesium Stearate, NF (powder)	0.585	4.50
Purified Water USP*	17.550	135.00

*Purified water is removed during processing

The formulation of Example 1 was prepared as follows:
1. Weigh all ingredients and keep in moisture resistant containers until ready for use.
2. Measure water into a container. Mix povidone at medium speed until completely dissolved.
3. Add tranexamic acid, microcrystalline cellulose (MCC), pregelatinized corn starch, and colloidal silicon dioxide to the high shear mixer.
4. Mix using impeller only.
5. Mix for an additional time (impeller only). Add all of the povidone solution during this mixing step.
6. Mix until adequately granulated (impeller and chopper). Proceed only when desired granulation has been achieved. Add additional water if necessary.
7. Dry the granulation to moisture content of NMT 1.2%.
8. Pass the granulation through the oscillating granulator equipped with a #30 mesh screen. Weigh the granulation. Add granulation to the V-Blender.
9. Add the hypromellose USP Methocel K3 Premium to the V-blender. Blend.
10. Pass magnesium stearate and stearic acid through oscillating granulator equipped with a #40 mesh screen. Add magnesium stearate and stearic acid to the V-blender and blend.
11. Perform specified physical property testing. Proceed to compression.
12. Compress tablets to desired weight.

Example 2

In Example 2, immediate release 650 mg tranexamic acid tablets were prepared having the ingredients listed in Table 2 below:

TABLE 2

Ingredient	Quantity per batch (kg)	Quantity per tablet (mg)
Active Ingredient		
Tranexamic Acid, EP (650 mg/tab)	84.50	650.0
Inactive Ingredients		
Microcrystalline Cellulose, NF (Avicel PH 101)	5.753	44.25
Microcrystalline Cellulose, NF (Avicel PH 102)	10.660	82.00
Colloidal Silicon Dioxide, NF	0.0975	0.75
Pregelatinized Corn Starch, NF	6.435	49.50
Croscarmellose Sodium, NF	19.50	15.00
Povidone, USP (K value range 29-32)	4.680	36.00
Stearic Acid, NF (powder)	2.340	18.00
Magnesium Stearate, NF (powder)	0.585	4.50
Purified Water, USP*	17.550	135.00
Film Coating (Inactive Ingredients)**		
Opadry White YS-1-7003	4.110	—
Purified Water, USP	36.990	—

*Purified water is removed during processing
**6 kg excess prepared to account for losses during transfer

The formulation of Example 2 was prepared as follows:
1. Weigh all ingredients and keep in moisture resistant containers until ready for use.
2. Measure water into a container. Mix povidone at medium speed until completely dissolved.
3. Add tranexamic acid, microcrystalline cellulose (MCC), pregelatinized corn starch, and colloidal silicon dioxide to the high shear mixer.
4. Mix using impeller only.
5. Mix for an additional time (impeller only). Add all of the povidone solution during this mixing step.
6. Mix until adequately granulated (impeller and chopper). Proceed only when desired granulation has been achieved. Add additional water if necessary.
7. Dry the granulation to moisture content of NMT 1.2%.
8. Pass the granulation through the oscillating granulator equipped with a #30 mesh screen. Weigh the granulation. Add granulation to the V-Blender.
9. Add the croscarmellose sodium and MCC to the V-Blender and blend.
10. Pass magnesium stearate and stearic acid through oscillating granulator equipped with a #40 mesh screen. Add magnesium stearate and stearic acid to the V-blender and blend.
11. Perform specified physical property testing. Proceed to compression.
12. Compress tablets.
12. After compression, spray coat the compressed dosage forms with the Opadry White in water.

Example 3

In Example 3, modified release 650 mg tranexamic acid tablets were prepared as in Example 1 and coated with a film coating similar to the immediate release tablets of Example 2. The ingredients are listed in Table 3 below:

TABLE 3

Ingredient	Quantity per batch (kg)	Quantity per tablet (mg)
Active Ingredient		
Tranexamic Acid, EP	84.50	650.0
Inactive Ingredients		
Microcrystalline Cellulose NF (Avicel PH 101)	5.753	44.25
Colloidal Silicon Dioxide NF	0.0975	0.75
Pregelatinized Corn Starch, NF	6.435	49.50
Hypromellose, USP (Methocel K3 Premium LV)	19.110	147.00
Povidone, USP (K value range 29-32)	4.680	36.00
Stearic Acid, NF (powder)	2.340	18.00
Magnesium Stearate, NF (powder)	0.585	4.50
Purified Water USP*	17.550	135.00
Film Coating (Inactive Ingredients)**		
Opadry White YS-1-7003	4.305	—
Purified Water, USP	38.750	—

*Purified water is removed during processing
**6 kg excess prepared to account for losses during transfer

Example 4

Bioavailability and Bioequivalence Evaluation

In Example 4, a comparative, randomized, single dose, 4-way Crossover Absolute Bioavailability (BA) and Bioequivalence (BE) study of Tranexamic Acid Tablet Formulations prepared in accordance with Examples 1 and 2 in

Healthy Adult Women Volunteers under Fasting Conditions was performed. The objective was to assess the bioequivalence of a 650 mg modified release tablet formulation prepared in accordance with Example 1 compared to the immediate release reference tablet formulation of tranexamic acid prepared in accordance with Example 2, and to determine the bioavailability of the modified tablet formulation to the approved IV (1 g) formulation Cyklokapron® by Pharmacia & Upjohn. The design was a randomized, 4-way crossover, comparative BE and BA determination. All oral doses administered were 1.3 g. Twenty-eight (28) healthy non-smoking adult female volunteer subjects were enrolled in the study. Sample size was calculated assuming a 25% CV in AUC_{inf}. The study endpoints were the 90% confidence intervals of the ratio of least-squares means of the pharmacokinetic parameters AUC_{0-t}, AUC_{inf} and C_{max} of the modified release formulation to the immediate-release formulation from serum concentration-time data drawn up to 36 hours after a single dose of drug. In addition, the bioavailability of the tablet formulations were calculated. Smokers, oral contraceptive users, those with a previous history of thromboembolic events and altered vision were excluded from the study. ECG monitoring was performed before, during and after the estimated times of peak serum tranexamic acid concentrations exposure. Adverse events were captured and recorded throughout the trial period.

In the study, subjects were randomized to receive single oral 1.3 g (2×650 mg tablets) dose of tranexamic acid in tablet forms which included a modified release dosage form and an immediate release dosage form. Subjects were also administered a single 1 g (10 ml) IV solution of tranexamic acid (100 mg/ml concentration).

A summary of the pharmacokinetic results from the study of Example 4 are listed in the tables below.

TABLE 4

Summary of Results - Tranexamic Acid in Plasma Pharmacokinetic Parameters (N = 26)

	ln AUC 0-t* (mcg · h/mL)	ln AUCinf* (mcg · h/mL)	ln Cmax* (mcg/mL)
Modified Release formulation			
Mean	66.703	69.642	11.251088
CV	26.8	27.2	29.1
N	26	24	26
Immediate Release formulation			
Mean	70.157	72.656	12.260414
CV	16.2	16.4	23.0
N	26	24	26
Least-Squares Mean:			
Modified Release	66.935	68.891	11.321919
Immediate Release	70.051	72.411	12.258222
Ratio of Least-Squares Mean (modified release/immediate release)%	95.6	95.1	92.4

*For In-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported. AUCinf, kel, half-life and F could not be estimated for some subjects. AUG 0-t is the area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.

TABLE 5

Summary of Results - Tranexamic Acid in Plasma Pharmacokinetic Parameters (N = 26)

	Tmax (h)	Half-life (h)	kel (1/h)	F (%)
Modified Release formulation				
Mean	2.942	11.370	0.06300	44.93
CV	22.7	17.6	19.4	25.3
n	26	26	26	24
Immediate Release formulation				
Mean	2.808	11.013	0.06438	46.04
CV	20.8	15.5	15.3	16.1
n	26	24	24	24

TABLE 6

Summary of Results - Tranexamic Acid in Plasma Pharmacokinetic Parameters (N = 26)

	Ln AUC 0-t* (mcg · h/mL)	ln AUCinf* (mcg · h/mL)	ln Cmax* (mcg/mL)
90% Confidence Intervals (Modified release/Immediate release) %			
lower limit:	87.8%	87.4%	84.0%
upper limit:	104.0%	103.5%	101.6%
p-Value (ANOVA)			
Modified vs Immediate	0.3721	0.3259	0.1676
Period	0.0704	0.0499	0.0356
Sequence	0.7734	0.7978	0.8207
Intrasubject CV %	18.3	17.4	20.6

*For In-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported. AUCinf, kel, half-life and F could not be estimated for some subjects.

Concentration-time profiles for the study of Example 4 are presented on semi-log and linear scale over 36 hours and are depicted in FIGS. **3** and **4**.

The following pharmacokinetic parameters in the table below were calculated for tranexamic acid in plasma for the study of Example 4.

MRT: The mean residence time (MRT) after intravenous administration of tranexamic acid was determined using the equation,

AUMC/AUC+infusion time/2,

where the AUMC is the area under the moment-time curve.

MTT: Following oral administration of the Modified Release and Immediate Release formulations, the mean transit time (MTT) of tranexamic acid was calculated by dividing the AUMC by the AUC.

MAT: The mean absorption time (MAT) for the two formulations was derived by subtracting the MRT from the MTT.

Mean (±SD) results are presented in the table below:

TABLE 7

	IV	Modified Release	Immediate Release
MRT (hours)	3.51 ± 0.38	N/A	N/A
MTT (hours)	N/A	7.70 ± 0.72	7.21 ± 1.01
MAT (hours)	N/A	4.18 ± 0.70	3.70 ± 0.94

The mean transit time (MTT) and mean absorption time (MAT) of the Modified Release formulation of tranexamic acid was approximately 30 minutes longer than that observed for the Immediate Release formulation.

The most frequently reported adverse events from the study of Example 4 are listed in the table below. The table lists the number of subjects reporting adverse events, and the percentage of subjects is in parentheses.

TABLE 8

	Treatment		
Adverse Events	Modified Release (2 × 650 mg) (n = 27)	Immediate Release (2 × 650 mg) (n = 27)	IV solution (10 × 100 mg/ml) (n = 27)
Headache	4 (15%)	7 (26%)	7 (26%)
Nausea	0 (0%)	2 (7%)	10 (37%)
Dizziness	0 (0%)	0 (0%)	11 (41%)
Feeling Hot	0 (0%)	0 (0%)	6 (22%)
Nasal Congestion	2 (7%)	1 (4%)	1 (4%)
Cough	0 (0%)	0 (0%)	2 (7%)
Urine odor abnormal	2 (7%)	0 (0%)	1 (4%)

Dissolution Results for Immediate Release and Modified Release Formulations prepared in accordance with Examples 2 and 1 respectively used in the study of Example 4 tested under USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. are listed in the tables below.

TABLE 9

Test Results for the Immediate Release Formulation in Table 2.

	%	RSD
Assay	99.9%	
Content Uniformity	99.4%	0.7%
Unknown Related Substance	NMT 0.2% Each	<0.1%
Total Related Substances and Impurities	NMT 2.0% Total	<0.1%
Dissolution Profile		
15 min.	58.0%	
30 min.	96.0%	
45 min.	102.0%	
60 min.	104.0%	

TABLE 10

Test Results for the Modified Release Formulation in Table 1

	%	RSD
Assay	99.4%	
Content Uniformity	98.5%	0.6%
Unknown Related Substance	NMT 0.2% Each	<0.1%
Total Related Substances and Impurities	NMT 2.0% Total	<0.1%

TABLE 10-continued

Test Results for the Modified Release Formulation in Table 1

	%	RSD
Dissolution Profile		
15 min.	21.0%	
30 min.	40.0%	
45 min.	58.0%	
60 min.	73.0%	
90 min.	98.0%	

Conclusions

The ratios of least-squares means and the 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC_{0-t}, AUC_{inf} and C_{max} for tranexamic acid in plasma were within the 80-125% Food and Drug Administration (FDA) acceptance range for the modified release formulation versus the immediate release formulation under fasting conditions.

The absolute bioavailability of the modified release and immediate release tablet formulations were 44.93% and 46.04% respectively.

Based on these results, the modified release tranexamic acid tablet formulation and the immediate release tranexamic acid formulation are bioequivalent under fasting conditions.

Example 4A

Comparative Example

Comparative Example 4A, a 500 mg immediate release tranexamic acid tablet, approved and marketed in Canada under the name Cyklokapron was obtained and dissolution tested under USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C. The dissolution results are listed in Table 10A below:

TABLE 10A

Sample #	% dissolved in 15 min.	% dissolved in 30 min.	% dissolve in 45 min.	% dissolved in 60 min.
1	102	104	105	106
2	102	104	105	106
3	101	102	102	105
4	99	101	102	103
5	100	102	103	104
6	99	101	102	104
Average	101	102	103	105
% RSD	1.4	1.3	1.4	1.1

Example 5

In Example 5, based on single dose pharmacokinetic parameters, pharmacokinetic simulations of serum concentrations were performed to compare dosing the modified release formulation of Example 4 at every 8 hours (Q8H: at 6:00 AM, 2:00 PM, 10:00 PM) and dosing three times a day, other than every 8 hours (TID: at 8:00 AM, 2:00 PM, and 10:00 PM). The results are provided in Tables 11-14 below.

TABLE 11

Tranexamic Acid - Modified Release Formulation
Dosage Regimen Simulation - ORAL
1.3 g q8hr

Time (h)	Dose(mcg)	Conc.(mcg/mL)
0	1.30E+06	0
1	0	4.0594
2	0	10.0551
3	0	10.6433
4	0	9.20306
5	0	7.26932
6	0	5.4699
8	1.30E+06	2.89909
9	0	6.15391
10	0	11.5813
11	0	11.7752
12	0	10.0646
13	0	7.94622
14	0	6.02067
15	0	4.4712
16	1.30E+06	3.30248
17	0	6.51406
18	0	11.9097
19	0	12.0794
20	0	10.3495
21	0	8.21523
22	0	6.2761
23	0	4.71463
24	1.30E+06	3.53505
25	0	6.73663
26	0	12.1229
27	0	12.2838
28	0	10.5455
29	0	8.40336
30	0	6.45664
31	0	4.88791
32	1.30E+06	3.70138
33	0	6.89628
34	0	12.2762
35	0	12.4309
36	0	10.6868
37	0	8.53894
38	0	6.5868
39	0	5.01286
40	1.30E+06	3.82133
41	0	7.01144
42	0	12.3867
43	0	12.537
44	0	10.7887
45	0	8.63675
46	0	6.68069
47	0	5.103
48	1.30E+06	3.90786
49	0	7.09451
50	0	12.4665
51	0	12.6136
52	0	10.8621
53	0	8.70731
54	0	6.74842
55	0	5.16802
56	1.30E+06	3.97028
57	0	7.15443
58	0	12.524
59	0	12.6688
60	0	10.9152
61	0	8.7582
62	0	6.79728
63	0	5.21493
64	1.30E+06	4.01531
65	0	7.19766
66	0	12.5655
67	0	12.7087
68	0	10.9534
69	0	8.79492
70	0	6.83253
71	0	5.24877
72	1.30E+06	4.0478
73	0	7.22885
74	0	12.5954

TABLE 11-continued

Tranexamic Acid - Modified Release Formulation
Dosage Regimen Simulation - ORAL
1.3 g q8hr

Time (h)	Dose(mcg)	Conc.(mcg/mL)
75	0	12.7374
76	0	10.981
77	0	8.82141
78	0	6.85796
79	0	5.27318
80	1.30E+06	4.07124
81	0	7.25135
82	0	12.617
83	0	12.7581
84	0	11.0009
85	0	8.84052
86	0	6.87631
87	0	5.29079
88	1.30E+06	4.08814
89	0	7.26758
90	0	12.6326
91	0	12.7731
92	0	11.0153
93	0	8.8543
94	0	6.88954
95	0	5.3035
96	1.30E+06	4.10034
97	0	7.27929
98	0	12.6439
99	0	12.7839
100	0	11.0256
101	0	8.86425
102	0	6.89909
103	0	5.31266
104	1.30E+06	4.10913
105	0	7.28773
106	0	12.652
107	0	12.7917
108	0	11.0331
109	0	8.87142
110	0	6.90597
111	0	5.31927
112	1.30E+06	4.11548
113	0	7.29382
114	0	12.6578
115	0	12.7973
116	0	11.0385
117	0	8.8766
118	0	6.91094
119	0	5.32404
120	0	4.12006

Concentration-time profiles are presented over 120 hours for the modified release formulation in Table 12 and are depicted in FIG. **1**. A 1 g formulation administered q8 h is also depicted for comparison purposes.

TABLE 12

Cmax, Cmin and Cavg for 1.3 g q8 hr simulation
Simulation at 120 hours

Pharmacokinetic Parameter	Concentration
Cmax	12.8 mcg/mL
Cmin	4.1 mcg/mL
Cavg	8.4 mcg/ml

TABLE 13

Tranexamic Acid - Modified Release Formulation
Dosage Regimen Simulation - ORAL
1.3 g TID (8:00 AM, 2:00 PM, and 10:00 PM)

Time (h)	Dose(mcg)	Conc. (mcg/mL)
0	1.30E+06	0
1	0	4.0594
2	0	10.0551
3	0	10.6433
4	0	9.20306
5	0	7.26932
6	1.30E+06	5.4699
8	0	12.9542
9	0	12.7378
10	0	10.7293
11	0	8.40129
12	1.30E+06	6.33141
13	0	8.74352
14	0	13.505
15	0	13.2018
16	0	11.1327
17	0	8.76144
18	0	6.65976
19	0	4.98823
20	0	3.73474
21	0	2.8275
22	0	2.18502
23	0	1.73555
24	1.30E+06	1.42243
25	0	5.26298
26	0	11.104
27	0	11.5807
28	0	10.058
29	0	8.06103
30	1.30E+06	6.21137
31	0	8.76659
32	0	13.6187
33	0	13.3709
34	0	11.334
35	0	8.97998
36	1.30E+06	6.88576
37	0	9.27495
38	0	14.0147
39	0	13.6908
40	0	11.6019
41	0	9.21185
42	0	7.09208
43	0	5.40321
44	0	4.1331
45	0	3.20991
46	0	2.55212
47	0	2.08796
48	1.30E+06	1.76074
49	0	5.58776
50	0	11.4158
51	0	11.88
52	0	10.3453
53	0	8.33688
54	1.30E+06	6.47618
55	0	9.02081
56	0	13.8627
57	0	13.6052
58	0	11.5589
59	0	9.1959
60	1.30E+06	7.09304
61	0	9.47395
62	0	14.2057
63	0	13.8742
64	0	11.778
65	0	9.38036
66	0	7.25433
67	0	5.55898
68	0	4.28264
69	0	3.35346
70	0	2.68993
71	0	2.22026
72	1.30E+06	1.88775
73	0	5.70968
74	0	11.5329

TABLE 13-continued

Tranexamic Acid - Modified Release Formulation
Dosage Regimen Simulation - ORAL
1.3 g TID (8:00 AM, 2:00 PM, and 10:00 PM)

Time (h)	Dose(mcg)	Conc. (mcg/mL)
75	0	11.9924
76	0	10.4532
77	0	8.44044
78	1.30E+06	6.57559
79	0	9.11625
80	0	13.9543
81	0	13.6931
82	0	11.6434
83	0	9.27696
84	1.30E+06	7.17086
85	0	9.54865
86	0	14.2775
87	0	13.943
88	0	11.8441
89	0	9.44431
90	0	7.31525
91	0	5.61745
92	0	4.33877
93	0	3.40735
94	0	2.74167
95	0	2.26992
96	1.30E+06	1.93543
97	0	5.75546
98	0	11.5768
99	0	12.0346
100	0	10.4937
101	0	8.47931
102	1.30E+06	6.61292
103	0	9.15208
104	0	13.9887
105	0	13.7261
106	0	11.6751
107	0	9.30739
108	1.30E+06	7.20008
109	0	9.5767
110	0	14.3044
111	0	13.9689
112	0	11.8689
113	0	9.46813
114	0	7.33811
115	0	5.63941
116	0	4.35985
117	0	3.42759
118	0	2.76109
119	0	2.28857
120	0	1.95333

Concentration-time profiles are presented over 120 hours for the modified release formulation in Table 14 and are depicted in FIG. 2. A 1 g formulation administered TID is also depicted for comparison purposes.

TABLE 14

Cmax, Cmin and Cavg for 1.3 g TID
(8:00 AM, 2:00 PM, and 10:00 PM)
Simulation at 120 hours

Pharmacokinetic Parameter	Conc.
Cmax	12.0, 14.0, 14.3 mcg/mL
Cmin	1.9, 6.6, 7.2 mcg/mL
Cavg	8.4 mcg/mL

Example 6

In Example 6, a study of a single dose followed by multiple doses, was performed on 20 healthy non-smoking adult female volunteers using a modified release formulation prepared in accordance with Example 1. After an overnight fast,

subjects received a single oral dose of tranexamic acid (1.3 g) on Day 1. Blood samples were taken before dosing and up to 36 hours post-dose. Subjects received another single oral dose of tranexamic acid (1.3 g) on the evening of Day 2, and 3 times a day (every 8 hours) starting on the morning of Day 3 until the last dose on the morning of Day 7. Blood samples were taken before the 6th, 9th, 12th and 15th dose (the last dose) for the determination of C_{min}, and up to 8 hours after the last dose, for the determination of drug concentration at steady-state. Subjects were housed from at least 10 hours before the 1st dose on Day 1 until after the 8-hour blood draw following the 15th dose (on Day 7).

Tranexamic acid is minimally bound (approximately 3%) to plasma proteins (mainly plasminogen) at "typical" therapeutic plasma concentrations of approximately 5-15 mg/L. The main route of elimination of tranexamic acid is renal glomerular filtration. After oral administration of tranexamic acid (250 or 500 mg) to healthy adults, between 40-70% of the administered dose is excreted unchanged in the urine within 24 hours. After IV administration (1 g) 30% of the dose is excreted unchanged in the urine within one hour, 45-55% within 2-3 hours and 90% within 24 hours.

The beta elimination half-life of tranexamic acid is 2 hours. Based on published data, the mean C_{max} and AUC_{0-6} pharmacokinetic parameters after a single 1.3 g oral dose of tranexamic acid are expected to be approximately 65% of those achieved with a 2 g dose (i.e. ~10 mg/L and ~40 mg-h/L, C_{max} and AUC_{0-6} under fasting conditions, respectively).

However, the pharmacokinetics of tranexamic acid were not adequately characterized in Pilbrant, et al., *Eur. J. Clin. Pharmacol*, (1981)-20:65-72, since blood samples were collected for up to only 6 hours post-dose. In addition, the plasma concentration-time curves after IV administration showed three exponential phases, with a gamma elimination half-life of approximately 7 hours. For this reason, the concentration-time profile of tranexamic acid was estimated by simulating the data over 36 hours, after oral administration of a 1.3 g dose under fasting conditions, using NONMEM. Based on the simulation results, it would be appropriate to collect blood samples until 36 hours in order to characterize the AUC, Cmax, tmax, t½ and F.

The objective of this study of Example 6 was to assess the pharmacokinetic linearity of the test tablet formulation of tranexamic acid (modified release), after a single oral dose (Day 1) compared to a daily (1.3 g every 8 hours) dosage regimen (Days 2 to 7), under fasting conditions.

In the study of Example 6, blood samples (1×5 mL) were collected in blood collection tubes containing lithium heparin at Hour 0 (pre-dose) on Day 1, and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 14, 24, 28, 32, and 36 hours post-dose. Blood samples for Cmin determinations were also collected immediately before the 6th, 9th, 12th, and 15th doses on Days 4, 5, 6, and 7, respectively, and at the following times after the 15th dose: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, and 8 hours. Plasma samples were separated by centrifugation, then frozen at −20° C.±10° C. and kept frozen until assayed at AAI Development Services in New-Ulm, Germany.

Noncompartmental Pharmacokinetic Parameters

Calculations for plasma tranexamic acid were calculated by noncompartmental methods using the following pharmacokinetic parameters in Tables 15 and 16:

Day 1:

TABLE 15

AUC 0-t:	The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.
AUCinf:	The area under the plasma concentration versus time curve from time 0 to infinity. AUCinf was calculated as the sum of AUC 0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.
AUC/AUCinf:	The ratio of AUC 0-t to AUCinf.
Cmax:	Maximum measured plasma concentration over the time span specified.
tmax:	Time of the maximum measured plasma concentration. If the maximum value occured at more than one time point, tmax was defined as the first time point with this value.
kel:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. This parameter was calculated by linear least squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g. three or more non-zero plasma concentrations).
t½:	The apparent first-order terminal elimination half-life was calculated as 0.693/kel.

No value for kel, AUCinf or t½ were reported for cases that did not exhibit a terminal log-linear phase in the concentration versus time profile.

Day 7:

TABLE 16

AUCτ:	The area under the plasma concentration versus time curve over the final dosing interval, as calculated by the linear trapezoid method.
Cmax:	Maximum measured plasma concentration over the final dosing interval.
Cmin:	Measured plasma concentration prior to the morning dose.
tmax:	Time of the maximum measured plasma concentration over the final dosing interval. If the maximum value occured at more than one time point, tmax was defined as the first time point with this value.
Flux:	Percent fluctuation was calculated as follows: Flux 1: $\frac{Cmax - Cmin}{Cssav} \times 100$ where Cssav was calculated as the ratio of AUC 0-τ to the dosing interval, τ Flux 2: $\frac{Cmax - Cmin}{Cmin} \times 100$

Compartmental Pharmacokinetic Parameters

Compartmental analysis was performed on tranexamic acid data following single and multiple oral administrations of the modified release (MR) tablet formulation. Multiple

compartmental models were constructed and their ability to fit plasma concentrations of tranexamic acid were evaluated using a standard two-stage (STS) approach with ADAPT-II (maximum likelihood analysis). The discrimination process was performed by computing the Akaike Information Criterion Test (AIC), the minimum value of the objective function (OBJ) and by looking at pertinent graphical representations of goodness of fit (e.g. fitted and observed concentrations versus time).

The final analysis was performed using an iterative two-stage approach with the IT2S® software. This software uses a population methodology which allows one to provide robust PK parameter estimates on an individual subject and population basis. All relevant pharmacokinetic parameters were calculated and reported. Concentrations were modeled using a weighting procedure of $W_j=1/S_j^2$ where the variance σ_j^2 was calculated for each observation using the equation $\sigma j^2=(a+b*Y_j)^2$ where a and b are the intercept and slope of each variance model. The slope is the residual variability associated with each concentration (includes the intra-individual variability and the sum of all experimental errors), and the intercept is related to the limit of detection of the analytical assay. All PK parameter estimates were updated iteratively during the population PK analysis (VARUP, IT2S®) until stable values were found. The analysis included the quantitative estimation of population PK parameters and interindividual variability of tranexamic acid in plasma.

Individual profiles of observed vs fitted plasma concentrations of tranexamic acid were provided for the MR formulation.

Statistical Analyses

Descriptive Statistics

Descriptive statistics including arithmetic means, standard deviations and coefficients of variation were calculated on the individual concentration and pharmacokinetic data. Additionally, geometric means were calculated for the parameters $AUC_{0-\tau}$, AUC_{inf}, and C_{max} for Day 1 and AUCτ, C_{max} and C_{min} for Day 7.

Time Dependence Pharmacokinetic Linearity

The pharmacokinetic parameter AUCτ (Day 7) was compared against AUC_{inf} (Day 1) using an analysis of variance (ANOVA) on the ln-transformed values for tranexamic acid. The ANOVA model included Group, Day (1 (AUC_{inf}) and 7 (AUCτ)) and the interaction Day*Group as fixed effects. All the interaction terms were not statistically significant, at a level of 5%, and were dropped from the final model. The ANOVA included calculation of least-squares means (LSM), the difference between Day LSM and the standard error associated with this difference. The above statistical analysis was done using the SAS® GLM procedure.

The ratio of LSM was calculated using the exponentiation of the Day LSM from the analysis on the ln-transformed response. The ratio was expressed as a percentage relative to AUC_{inf} (Day 1).

A ninety percent confidence interval for the ratio was derived by exponentiation of the confidence interval obtained for the difference between Day LSM resulting from the analysis on the ln-transformed response. The confidence interval was expressed as a percentage relative to AUC_{inf} (Day 1).

Steady-State Analysis

A steady-state analysis was performed, on the ln-transformed pre-dose Cmin concentrations at −72, −48, −24 and 0-hour time points, using Helmert's contrasts. The ANOVA model included Group, Time and the interaction Time*Group as fixed effects. In order to model the correlations within every subject, an appropriate variance-covariance matrix was chosen among the following: unstructured (UN), compound symmetry (CS), compound symmetry heterogeneous (CSH), variance component (VC), autoregressive (AR(1)), autoregressive heterogeneous (ARH(1)) and autoregressive moving average (ARMA(1,1)), using the Akaike's Burnham and Anderson criterion (AICC). All the interaction terms were not statistically significant, at a level of 5%, and were dropped from the final model. The ANOVA included also calculation of least-squares means (LSM) for each pre-dose C_{min} concentrations. Helmert's contrasts were constructed such that each time point is compared to the mean of subsequent time points. There are 3 contrasts associated to the 4 pre-dose concentration timepoints. They are listed in Table 17 below:

TABLE 17

Contrast	Tests
Compar. 1	Predose Day 4 compared to (mean predose of Day 5, 6 and 7)
Compar. 2	Predose Day 5 compared to (mean predose of Day 6 and 7)
Compar. 3	Predose Day 6 compared to predose Day 7 (0-hour)

The above statistical analyses were done using the SAS® Mixed procedure.

Formulae

The following formulae in Table 18 were used for the ratio of least-squares means and 90% confidence interval calculations derived from the ANOVA on the ln transformed pharmacokinetic parameters.

TABLE 18

Ratio of Least-squares Means:	$100 \times e^{(LSM_{Day\ 7} - LSM_{Day\ 1})}$
90% Confidence Interval:	$100 \times e^{(LSM_{Day\ 7} - LSM_{Day\ 1} \pm t_{df,0.05} \times SE_{Day\ 7-Day\ 1})}$

Note:

$LSM_{Day\ 7}$ and $LSM_{Day\ 1}$ are the least-squares means of Day 7 and Day 1, as computed by the LSMEANS statement of the SAS ® GLM procedure.

$t_{df,\alpha}$ is the value of the Student's t distribution with df degrees of freedom (i.e. degrees of freedom for the error term from the analysis of variance) and a right-tail fractional area of α (α = 0.05).

$SE_{Day\ 7-Day\ 1}$ is the standard error of the difference between the adjusted Day means, as computed by the ESTIMATE statement in the SAS ® GLM procedure.

Discussion of Pharmacokinetic Results

Time Dependence Pharmacokinetic Linearity

The ANOVA model included Group, Day (1 (AUC_{inf}) and 7 (AUCτ)) and the interaction Day*Group as the fixed effect. All the interaction terms were not statistically significant, at a level of 5%, and were dropped from the final model. Pharmacokinetic linearity was calculated for the formulation using the same approach as above, but the ANOVA model included Group, Day 1 (AUCinf) and Day 7 (AUCτ)) and the interactions Group*Day as fixed effects and Subject nested within Group as a random effect.

The pharmacokinetic linearity results are summarized in the table below.

TABLE 19

		90% Confidence Interval	
Formulation	Ratio AUCτ/AUCinf	Lower Limit	Upper Limit
MR	97.3	86.5	109.5

The pharmacokinetic linearity results indicate that the ratios of least-squares means of AUCτ(Day 7) to AUC_{inf} (Day 1) and the 90% confidence interval for the MR formulation were within the 80-125% acceptance range. Based on these results, the 650 mg tranexamic acid modified release tablets

exhibited linear pharmacokinetics following repeated administration (7 days) of a 1.3 g dose under fasting conditions.

Steady-State Analysis

For the steady-state analysis, the CS variance-covariance matrix was chosen to model the correlations within every subject. Overall, the interaction term (i.e. Time*Group) was not statistically significant and was removed from the final ANOVA model. For each formulation, the same approach as above was used, but the ANOVA models included Group, Time and the interactions Time*Group as fixed effects.

A summary of LSM results for the steady-state analysis are summarized in Table 20A below.

TABLE 20A

Formulation	Days	Times (hour)	LSM derived from the ANOVA
MR	4	−72	4.90536
	5	−48	4.77323
	6	−24	5.23678
	7	0	5.15389

Summary of statistical comparisons for the steady-state analysis are summarized in Table 20B below

TABLE 20B

Formulation	Helmert's contrasts	P-value
MR	Predose Day 4 compared to (mean predose of Day 5, 6 and 7)	0.4438
	Predose Day 5 compared to (mean predose of Day 6 and 7)	0.0393
	Predose Day 6 compared to predose Day 7	0.7318

Based on the results above, steady-state plasma concentration of tranexamic acid were reached on Day 4 (−72-hour), since the p value for the first contrast was not statistically significant at a 5% alpha error. It should be noted that the second comparison [Predose Day 5 compared to (mean of Day 6 and 7)] was found to be statistically significant.

The largest difference observed in predose plasma concentrations of tranexamic acid between the LSM of predose Day 5 compared to Day 6 and 7 was less than 10%, which is not considered clinically relevant. Moreover, the last contrast was not statistically significant and the observed difference between the LSM of predose Day 6 and 7 was less than 2%.

Compartmental Pharmacokinetic Analysis

The mean apparent oral clearance (CL/F) of the MR formulation calculated with compartmental methods was 17.7 L/h (295 mL/min). Based on previous data reported in the literature, the group of Pilbrant, et al., have determined that the urinary recovery of tranexamic acid exceeded 95% of the dose administered. Considering the bioavailability of the MR formulation (Mean F: 44.9%, See Table 5), the systemic clearance (CL) of tranexamic acid (295 mL/min×0.449=123 mL/min) would be close to the glomerular filtration rate in healthy subjects (125 mL/min)5.

Using compartmental methods, the mean T½γ for the MR formulation was 16.6 hours. Similar values of terminal elimination half-life were previously reported in the literature. Pilbrant A., et al., *Eur. J. Clin. Pharmacol* (1981), 20: 65-72.

Following a single oral dose of 1.3 g of the MR formulation, the mean plasma concentrations of tranexamic acid observed at 28, 32, and 36 hours were 0.19724, 0.15672, and 0.13624 mcg/mL, respectively. Considering the therapeutic window of tranexamic acid (5-15 mcg/mL) and the very low plasma concentration levels observed at these timepoints, the terminal elimination half-life (T½γ) characterizing the slow decline of plasma concentrations should not play a clinically significant role in the frequency of drug administration.

Pharmacokinetic Conclusions

The pharmacokinetic linearity results indicate that the ratios of least-squares means of AUCτ (Day 7) to AUCinf (Day 1) and the 90% confidence interval for the MR formulation were within the 80-125% acceptance range. Based on these results, the 650 mg tranexamic acid modified release tablets exhibited linear pharmacokinetics following repeated administration (7 days) of a 1.3 g dose under fasting conditions.

Steady-state plasma concentrations of tranexamic acid for the modified-release tablets were reached on Day 4 (−72-hour), since the p-value for the first contrast was not statistically significant at a 5% alpha error.

The pharmacokinetics of tranexamic acid was properly described using a three compartment PK model with linear elimination. The absorption kinetic of the single-dose (Day 1) data of tranexamic acid for the MR formulation was best described using a mixed-order rate constant of absorption.

Plasma Pharmacokinetic Parameters for the modified release (MR) formulation of Tranexamic Acid on day 1 are listed in Table 21 below.

TABLE 21

	In AUC_{0-t}* (mcg · h/ml)	In AUC_{inf}* (mcg · h/ml)	In C_{max}* (mcg/ml)	T_{max} (h)	Half-life (h)	K_{el} (1/h)
Mean	74.571	76.875	13.176041	3.079	11.078	0.06443
CV %	31.3	30.4	33.1	25.0	16.9	18.3
N	19	19	19	19	19	19

*For In-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported; AUC_{0-t} = AUC post dose (0-36 hours)

Plasma Pharmacokinetic Parameters for the modified release (MR) formulation of Tranexamic Acid on day 7 are listed in Table 22 below.

TABLE 22

	In AUC_t* (mcg · h/ml)	In C_{max}* (mcg/mL)	In C_{min}* (mcg/ml)	T_{max} (h)	Flux 1** (%)	Flux 2** (%)
Mean	74.791	15.803509	5.157681	2.553	113.16	219.21
CV %	29.0	30.1	31.2	14.4	21.6	44.6
N	19	19	19	19	19	19

*For In-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported; AUC_t = AUC dosing interval (8 hours)
**Defined in Table 16

Conclusion

While the invention herein disclosed has been described by means of specific embodiments and applications thereof, numerous modifications and variations could be made thereto by those skilled in the art without departing from the spirit and scope of the present invention. Such modifications are understood to be within the scope of the appended claims.

What is claimed is:

1. A method of treating menorrhagia, the method comprising:

orally administering to a patient in need of such treatment a tranexamic acid formulation comprising:

tranexamic acid or a pharmaceutically acceptable salt thereof; and

a modified release material;

wherein the tranexamic acid or pharmaceutically acceptable salt thereof is present in an amount from about 50% to about 95% by weight of the formulation;

wherein the modified release material is present in an amount from about 5% to about 50% by weight of the formulation;

wherein the formulation is administered as two oral dosage forms, each providing a dose of about 650 mg of tranexamic acid; and

wherein said formulation provides an in-vitro dissolution release rate of the tranexamic acid or pharmaceutically acceptable salt thereof, when measured by a USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C., of less than about 40% by weight of the tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, less than about 70% by weight of the tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes and not less than about 50% by weight of the tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes.

2. The method of claim **1**, wherein said formulation provides an in-vitro dissolution release rate of the tranexamic acid or pharmaceutically acceptable salt thereof, when measured by the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C., of about 0% to about 40% by weight of the tranexamic acid or pharmaceutically acceptable salt thereof released at about 15 minutes, from about 20% to about 60% by weight of the tranexamic acid or pharmaceutically acceptable salt thereof released at about 30 minutes, from about 40% to about 65% by weight of the tranexamic acid or pharmaceutically acceptable salt thereof released at about 45 minutes, from about 50% to about 95% by weight of the tranexamic acid or pharmaceutically acceptable salt thereof released at about 60 minutes, and not less than about 60% by weight of the tranexamic acid or pharmaceutically acceptable salt thereof released at about 90 minutes.

3. The method of claim **1**, wherein the formulation releases about 10% to about 25% by weight of the tranexamic acid or pharmaceutically acceptable salt thereof every 15 minutes when measured in vitro utilizing the USP 27 Apparatus Type II Paddle Method @ 50 RPM in 900 ml water at 37±0.5° C.

4. The method of claim **1**, wherein the formulation releases about 1% of the tranexamic acid or pharmaceutically acceptable salt thereof every minute when measured in-vitro utilizing the USP 27 Apparatus Type II paddle method at 50 RPM in 900 ml water at 37±0.5° C.

5. The method of claim **1**, wherein the tranexamic acid or pharmaceutically acceptable salt thereof is tranexamic acid.

6. The method of claim **1**, wherein a mean maximum plasma concentration (C_{max}) of tranexamic acid of from about 5 to about 17.5 mcg/ml is provided following the administration.

7. The method of claim **1**, wherein the formulation is in the form of a matrix tablet which comprises a drug mixed together with a granulated modified release material.

8. The method of claim **1**, wherein the tranexamic acid or pharmaceutically acceptable salt thereof is present in an amount from about 60% to about 90% by weight of the formulation.

9. The method of claim **1**, wherein the tranexamic acid or pharmaceutically acceptable salt thereof is present in an amount from about 60% to about 80% by weight of the formulation.

10. The method of claim **1**, wherein the modified release material is present in an amount from about 10% to about 35% by weight of the formulation.

11. The method of claim **1**, wherein:

the tranexamic acid or pharmaceutically acceptable salt thereof is present in an amount from about 60% to about 90% by weight of the formulation;

the modified release material is present in an amount from about 10% to about 35% by weight of the formulation;

the formulation is in the form of a matrix tablet which comprises a granulated drug mixed together with the modified release material.

12. The method of claim **11**, wherein the tranexamic acid or pharmaceutically acceptable salt thereof is tranexamic acid.

* * * * *

PROOF OF SERVICE

I hereby certify that on May 1, 2014, copies of Defendant-Appellant's Opening Brief were served via CM/ECF upon the following:

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